MALIGNANT DISEASE OF THE URINARY TRACT *

Sir ERIC RICHES
M.C., M.S. Lond., F.R.C.S.

SURGEON AND UROLOGIST, THE MIDDLESEX HOSPITAL, LONDON, W.1

THE URETHRA

IN the discussion of carcinoma of the bladder stress was laid on the different behaviour of papillary and solid growths. In malignant growths of the urethra there is a similar duplicity of behaviour, but it depends more upon the situation of the tumour than on its histological structure.

Seven years ago Cullen and I reported 34 cases of urethral carcinoma (Riches and Cullen 1951); to those I can now add another.

The tumours fell into two groups, anterior and posterior; and there was evidence in some that the urethral growth was an implant from the bladder. Invasion of the inguinal glands had occurred in half and distant metastases in about a third.

Prognosis

There is a striking difference between the prognosis of the anterior and the posterior growths.

Only 2 out of the 9 patients with growths of the anterior urethra lived for *less* than three years: the remainder all passed the five-year mark. Only 2 patients had metastases; and 1 of these, whose inguinal glands were irradiated, is alive and well seven years later. By contrast, with tumours of the deep urethra the outlook is very bad. 19 out of 20 patients were dead within four years and 14 had metastases.

The increased liability to metastases is one of the reasons for the poor prognosis of deep tumours. Other factors are the lateness of the symptoms and failure to recognise them at a curable stage. In addition, the deep urethra is less accessible to treatment than the anterior part; and one may be reluctant to carry out a sufficiently radical extirpation for what appears to be a small localised tumour.

Treatment

For anterior urethral cancer in the male the best treatment is partial amputation of the penis. If radiotherapy is given in adequate dosage, the growth may be followed by stricture. In women diathermy excision followed by irradiation, either by radium implantation or by X rays, is satisfactory. In either sex suspicious glands in the groin should be subjected to biopsy, and, if invaded, treated by X rays or by block dissection.

For the vulvourethral growths in women wide excision with urinary diversion offers some hope; but they are generally better treated by irradiation with radium needles or applicators. Men with carcinoma of the bulbomembranous urethra often come too late for effective treatment. The story of a stricture, of perineal and later perineal suppuration and of nodules in the skin with invaded inguinal glands, is characteristic. Irradiation at this stage makes the infection worse: but I believe that a combination of well-timed radiotherapy and of surgery is still our best weapon.

Extension or implantation of a bladder growth into the urethra worsens the outlook: it lays the inguinal glands open to invasion and it promotes distant metastases. The urethral tumour may be discontinuous with the main growth, when it can be removed by a separate operation; but even a discrete papillary carcinoma of low malignancy will sometimes invade the inguinal glands. It would appear that confinement to the narrow tubular urethra encourages growth into the deeper tissues, whilst in the more spacious bladder there is room for surface expansion.

THE PENIS

Carcinoma of the penis is not common. Of 24 patients with malignant penile growths the youngest was thirty-two and the oldest eighty-three. The average age was sixty-one. There were only 17 admissions to the Middlesex Hospital in five years.

It is well known that the disease is exceedingly rare in those circumcised in infancy; and phimosis and its consequent lack of cleanliness are undoubtedly predisposing factors. I do not advocate universal circumcision, but if the pædiatricians who condemn the operation saw some of the patients later in life they might reconsider their attitude.

Types

Although it is one of the least malignant of the growths of the urinary tract, carcinoma of the penis obeys the rule and occurs in two main forms. The *papillary* type grows slowly into a large cauliflower-like excrescence with surface ulceration. Glands in the groin are enlarged by sepsis but rarely invaded by growth. The total removal of the organ can be followed by cure. The *ulcerative* type may be small; but it grows by infiltration of the underlying tissues, invasion of the inguinal glands, and sometimes by bloodborne spread through the cavernous spaces. A man with this lesion may be dead within two years. Thus, as in the bladder, the larger growths are often less malignant.

There are other types of which the intraepidermal carcinoma —known variously as Paget's disease, Bowen's disease, or erythroplasia of Queyrat—is considered to be precancerous. At an early stage it can be cured by X-ray therapy leaving a presentable member.

Treatment

Both surgery and irradiation have a part to play in treatment. Irradiation alone, either by X rays or by radium, will sometimes cure a small lesion; but the need for amputation after irradiation arose in 5 out of 8 cases. There is a natural desire to preserve the penis, and a patient may prefer a distorted member to none at all. In 3 patients a local excision only was done; and 1 of them has survived five years without recurrence. The other 2 are living after shorter periods. The more usual surgical treatment is partial amputation; this was the choice in more than half the patients. The need for total amputation is determined by the extent of the lesion; when the penis is almost completely destroyed, partial amputation is impossible. I no longer do the radical amputation but prefer biopsy of the inguinal glands at the time of the total or partial amputation, dealing with them subsequently if necessary. When the glands are invaded, irradiation should be the primary treatment;

* Based on the second of three Lettsomian lectures for 1958 delivered before the Medical Society of London.

TABLE I—RESULTS OF TREATMENT IN CARCINOMA OF PENIS

5-year survivals	13/13 (*100%*)
10-year survivals	2/4 (*50%*)
Died from the disease	1 at 2 years*
Died from other causes, without recurrence	4 (1 at 8 years, 1 at 7 years, 2 at 6 years)

*Operated upon in 1954 and therefore not yet a possible 5-year survivor.

but the need for a possible subsequent block dissection should be borne in mind.

After treatment of the glands, by whatever method, there is a tendency to œdema of the legs. This can persist for many months. The ingenious rotation flap devised by Lee (1955) may overcome the tendency to non-union of the skin, but it adds considerably to the operation. The other complication is meatal stenosis. This occurs almost exclusively after partial amputation, and especially when irradiation has been given before operation. It can be avoided by removing a disc of skin of the lower flap and by passing the urethra through this rather than through a stab wound. A $^1/_8$-inch projection of urethra looks ugly at the time, but eventually it leaves a rosette of mucosa with no constriction.

Cancer of the penis is the only carcinoma in the urinary tract which can boast a 100% five-year survival-rate (table I) (Savage 1957). Nevertheless, the 1 death in my series was from widespread pelvic deposits with compression of one ureter. The ulcerative type can show its truly malignant nature.

In partial amputation conservatism in the length of stump is desirable as sexual function may be preserved. On the other hand, I believe that total amputation should include removal of the testicles.

THE SCROTUM

Carcinoma of the scrotum is a dying disease which was formerly prevalent amongst chimney-sweeps, tar workers, gas workers, coalminers, and mule-spinners. During 1936–39 only 4 cases were admitted to the Middlesex Hospital, and there have been none since.

The primary growth should be treated by wide excision. Invaded inguinal lymph-glands may be removed by block-dissection, followed if necessary by irradiation. After irradiation the tissues in this region are devitalised and subsequent surgery is fraught with a grave danger of infection. The danger appears greater in scrotal than in penile cancers, although it exists in both.

THE PROSTATE

The prostate is the commonest site of malignant disease in the urinary tract: and it accounts for about 10% of all cancers in men. It is encountered in three main forms. Firstly, there is the patient in whom the diagnosis is certain from the hard, irregular, fixed, infiltrating tumour felt on rectal examination. Secondly, there is the latent or unsuspected carcinoma which has all the signs of benign hyperplasia but in which an area of carcinoma is found on histological examination after prostatectomy. Thirdly, the occult form may be present in the patient who comes complaining of lumbago or sciatica without urinary symptoms. He is often found to have widespread metastases.

Diagnostic Aids

The serum-acid-phosphatase level is raised in some 80% of patients with metastases; and a figure of 10 King-Armstrong units is diagnostic of metastatic prostatic carcinoma. With bone metastases the serum alkaline phosphatase is also raised, but this is not specific for prostatic tumours. The administration of œstrogens will lower these figures: if therefore the test is to be of help in diagnosis, blood must be taken before treatment is started.

A prostatic biopsy can be performed by the transurethral route, with a needle through the perineum, or by open perineal excision. Transrectal biopsy is also used in some centres. A positive result is diagnostic; but in an early case it is difficult to remove the right nodule. False negatives are not uncommon. I have been somewhat disappointed by the results of immediate section at the time of operation; more than once the clinical impression of malignancy was more accurate than the histological picture given by rapid staining.

The recent science of exfoliative cytology has also been used as a diagnostic aid. In the examination of the fluid expressed by prostatic massage the experience of the pathologist is of paramount importance. The diagnostic opinions of Prof. J. Bamforth, who has examined the secretion from many of my patients, have been of very great value. Despite these modern aids, however, diagnosis still rests on the result of a careful rectal examintion. Early detection is the only way in which cases suitable for radical prostatectomy with a prospect of complete cure can be found.

Treatment

Surgical

The theoretically ideal form of surgery is total prostatectomy, including removal of the prostatic capsule, the seminal vesicles, and the base of the bladder. Because of early infiltration this ideal is attainable in only about 5–10% of cases. In some American clinics a higher operability-rate is claimed, and this is used to encourage the routine annual rectal examination of all men over forty. Whether this form of control will ever be accepted here is open to doubt.

Radical prostatectomy can be done by the retropubic or the perineal route. Its chief disadvantage is its liability to be followed by urinary incontinence: its chief merit is a high potential cure-rate. Kimborough (1956) reported the five-year survival of 36 out of 56 patients so treated.

Simple prostatectomy by the retropubic, suprapubic, or perineal route will not completely remove the clinically manifest malignant prostate. Sometimes digital removal of such glands is impossible, but usually they can be excised with diathermy. For such cases, however, which almost break the surgeon's finger, transurethral resection offers a good alternative, provided the instrument can be introduced and provided enough tissue can be removed to relieve the obstruction. For latent carcinomas open prostatectomy has the advantage over transurethral resection in that complete removal of the malignant areas is more likely. Where there is reasonable doubt about the diagnosis I prefer the retropubic operation to transurethral resection. A preliminary course of stilbœstrol sometimes makes the operation easier.

The frequent origin of cancer in the posterior lobe or in the peripheral zone of the gland makes it imperative to remove the posterior capsule, rather than to enucleate the adenoma, in all prostatectomies. After enucleation of a histologically benign adenoma recurrence as a prostatic carcinoma is not unknown: I have records of 10 such cases.

After enucleation of the gland I now excise the posterior capsule with the diathermy needle; the trigonectomy is continued downwards with the sheet of tissue covering the seminal vesicles. The seminal vesicles are removed too if they are adherent. This part is examined separately. In a recent case the prostate showed benign hypertrophy, whilst the

posterior lobe and its capsule contained infiltrating adenocarcinoma.

Hormone Control

Stimulation of the prostate by androgens can be reduced by castration or by giving œstrogens. Nesbit and Baum (1950) collected statistics of about a thousand cases treated by one or other method alone, and by the two together, comparing them with a control group of untreated patients. The figures showed the longest survival in patients under the combined treatment with castration and œstrogens.

Castration sounds abhorrent, but the operation is one of subcapsular orchidectomy which leaves something in the scrotum that is scarcely distinguishable from the atrophied testes resulting from œstrogens. The patient is told that the operation will alter the secretion of the testicle. It has many advantages for the man who cannot or will not take œstrogens, or who forgets to do so. It also allows a lower dosage with consequent lessened side-effects. I believe that it should be an essential part of the treatment of every carcinoma of the prostate except in the latent cases with a small central area of cancer.

Œstrogens act by inhibiting pituitary gonadotrophin, which stimulates the testes. It has been claimed recently that stilbœstrol has a local cytostatic effect as well, and in its phosphorylated form (' Honvan ') it is said to have an enhanced therapeutic action when given intravenously (Hasche-Klünder and Wilmanns 1957). In a trial on a few cases I have not found such an improvement; and the serum acid phosphatase has tended to rise rather than to fall, at least in the advanced cases. ' Tace ', another proprietary œstrogen, is said to be stored in the fat and to give less troublesome side-effects.

The initial dose of stilbœstrol may be as small as 3 mg. a day, increasing to 15 mg. a day, although Fergusson and Franks (1953) have shown that 100 mg. is equally well tolerated and more effective. I agree that this is so; but I prefer to withhold higher doses until a clinical failure to respond demands them. A maintenance dose is required indefinitely: many patients have relapsed because the drug has been discontinued owing to an apparent " cure ".

The common side-effects of stilbœstrol—testicular atrophy, impotence, breast changes—can be disquieting to the patient; but they are seldom severe enough to warrant discontinuance of treatment. Of more serious import is the occasional case of fluid retention with œdema; some men with cardiac disease are forced to abandon the drug. Again orchidectomy provides the alternative.

Cortisone, which inhibits the production of adrenocorticotrophic hormone by the pituitary, has a place in treatment: in some patients it will relieve the pain of bone metastases.

Adrenalectomy and Hypophysectomy

Enlargement of the adrenals with an increased production of androgens may follow testicular atrophy; but the effects of bilateral adrenalectomy are not so dramatic as in carcinoma of the breast. Scott (1956) states that it should be considered only if the patient has androgen metabolites in the urine whilst on a dose of 100 mg. of cortisone daily.

Methods of destruction of the pituitary by irradiation, ablation, or division of its stalk are on trial. No large series of results has yet been reported.

Irradiation

X-ray therapy was a useful ancillary method before the days of stilbœstrol and we are starting to use it again in patients with bony metastases. Prostatic injections of radioactive colloidal gold have also been tried, but there is a danger of producing severe proctitis. Most of the gold, moreover, escapes into the blood-stream during the first few minutes, into the urine during the first few hours, and into the lymphatics within the first few days (Kerr et al. 1957).

Results

The prognosis of cancer of the prostate before the days of hormone control depended largely on its spread, on its degree of malignancy, and on the amount of urinary obstruction and renal damage it was causing. In 1943 in a series of 70 patients treated by transurethral resection and X rays, I found an average duration of life in clinically manifest cases of nearly two years; 1 patient lived for five years. In latent or unsuspected cases, treated by prostatectomy and X-ray therapy, the average survival was three years, 1 patient living for nearly ten years. The advent of hormone control has brought about a remarkable change. Although no patient can be said to have been completely cured, length of survival, relief of urinary obstruction, and the ability to lead an active life with freedom from pain are all greatly increased.

I have not attempted to estimate percentage survivals: the time from first symptoms to first treatment is too variable and the final follow-up not sufficiently complete. I have, however, examined the records of 200 patients with a complete follow-up (table II), excluding those who had a malignant recurrence after simple prostatectomy. The oldest patient was ninety-two, the youngest forty-five; their average age was sixty-eight. 12 were over eighty when first seen.

TABLE II—SURVIVAL IN 200 CASES OF CARCINOMA OF PROSTATE

Less than 1 year	40
More than 3 years	93
" " 4 "	75
" " 5 "	53
" " 7 "	31
" " 10 "	10

In considering the long survivors we must separate those who had a small central area of carcinoma in an otherwise benign prostate. This was so in 3 of the ten-year survivors and 5 of those who lived for seven years.

One man of seventy-three with such a latent growth developed a local recurrence in the prostatic urethra five years after prostatectomy. For the next five years he took stilbœstrol; and he remained well until his death at eighty-three. In several the growth was histologically of low-grade malignancy or of limited extent; but in some it was extensive. One medical man had a hard fixed malignant prostate at the age of sixty-two. Transurethral resection of 11 g. prostatic tissue relieved his obstruction. The gland showed extensive invasive adenocarcinoma. He has had stilbœstrol, 5 mg. daily, ever since; and he is alive and well twelve years later. His serum acid phosphatase was never raised.

At the other end of the scale are the patients who have widespread osseous or lymphatic metastases when first seen, usually with a raised serum acid phosphatase. There were 51 who had such metastases before treatment was started (table III). Multiple secondaries in the lungs

TABLE III—SURVIVAL IN 51 CASES OF CARCINOMA OF PROSTATE WITH METASTASES

Less than 1 year	11
More than 1 year	40
" " 2 "	34
" " 3 "	18
" " 4 "	12
" " 5 "	9
" " 7 "	4
" " 8 "	2

not infrequently disappear on treatment with œstrogens. Bone metastases regress more slowly and the changes are more apparent in the less common osteolytic deposits which may show recalcification. Metastases in palpable lymph glands can disappear quite quickly. As a rule a high serum acid phosphatase denotes a bad prognosis. Its fall indicates a good response and new metastases produce a rise.

Subcapsular orchidectomy was done in 68 of the 200 patients. It is now our policy to use it more extensively. Half the patients still alive and only a quarter of those who died had had orchidectomy. The prognosis appears to be better in older patients, but I think the real explanation of this lies in a lower grade of malignancy. The average survival of the 12 octogenarians was two years and four months.

Conclusion

Prostatic carcinoma differs from the disease in other parts of the urinary tract in being influenced and controlled by naturally occurring hormones. It is the first form of cancer to respond to treatment by oral medication; let us hope that there will soon be others.

REFERENCES

Fergusson, J. D., Franks, L. M. (1953) *Brit. J. Surg.* **40**, 422.
Hasche-Klünder, R., Wilmanns, H. (1957) *Brit. J. Urol.* **29**, 20.
Kerr, W. K., MacDonald, J. C. F., Smythe, C. A., Comet, V. (1957) *Canad. J. Surg.* **1**, 63.
Kimborough, J. C. (1956) *J. Urol.* **76**, 287.
Lee, E. S. (1955) *Lancet*, ii, 520.
Nesbit, R. M., Baum, W. C. (1950) *J. Amer. Med. Ass.* **143**, 1317.
Riches, E. W. (1943) *J. Fac. Radiol.* **16**, 187.
— Cullen, T. H. (1951) *Brit. J. Urol.* **23**, 209.
Savage, C. R. (1957) *ibid.* **29**, 69.
Scott, W. W. (1956-57) Year Book of Urology. Chicago.

COMPARISON OF ANIMAL AND VEGETABLE FATS IN INCREASING BLOOD COAGULABILITY

G. A. McDONALD
M.B. Aberd.
LECTURER IN MEDICINE
H. W. FULLERTON
M.D. Aberd., F.R.C.P.
REGIUS PROFESSOR OF MEDICINE
UNIVERSITY OF ABERDEEN

WE have shown previously that, after the ingestion of a meal of high animal-fat content, there occurs a shortening of the "accelerated clotting-time" (using plasma and Russell-viper venom) and of the clotting-time of whole blood in silicone-coated tubes (Fullerton et al. 1953). An increase in coagulability after a high-fat meal has been found by other workers (O'Brien 1956, 1958, Keys et al. 1957, Pilkington 1957). More recently, attempts have been made to determine whether this effect occurs equally after the ingestion of animal and vegetable fat. Unfortunately, published reports have been conflicting, and a study of these reports does not provide an obvious explanation for the variation in results. For example, O'Brien (1956), using the "accelerated clotting-time" with Russell-viper venom and platelet-poor plasma, found similar degrees of shortening after the ingestion of 50 g. butter, 50 g. margarine, and two eggs. On the other hand, Maclagan and Billimoria (1956) found a shortening of the "venom-time" after ingestion of 2 oz. butter, but not after the same amount of margarine. In addition they found that the "calcium-times" (method of Biggs and Macfarlane 1953) agreed with the "venom-times"—shortening after feeding butter but not margarine.

TABLE I—SIMULTANEOUS R.P.C. TIMES (SEC.) IN BOTH ARMS (NO DIFFICULTY IN VENEPUNCTURE)

Rt. arm	Lt. arm	Difference
125	111	14
117	112	5
129	123	6
108	114	6
109	112	3
108	110	2
92	89	3
105	105	0
103	101	2
122	123	1
96	98	2
100	99	1
95	98	3
88	90	2
91	94	3
		Mean 3·5

When these reports appeared we had already carried out a series of experiments which showed that ingestion of vegetable fat usually produced a shortening of the recalcified-plasma clotting-time of the same order as that which follows a meal of bacon, eggs, and butter. In view of the discrepancy between the findings of O'Brien and those of Maclagan and Billimoria, we extended our experiments in the hope of finding the reason for their conflicting conclusions. The issue appeared to us to be important since we have already adduced evidence to suggest that one factor related to the increasing incidence of cardiac infarction may be the increase in dietary fat (Fullerton 1955). Moreover the increase of dietary fat in this country in the past few decades has been due mainly to a greater intake of vegetable fat (Fullerton 1956).

Methods

All blood samples were obtained by dry-sterilised 5 ml. syringes (all-glass 'Vim') and needles (19 B.W.G. 1 in.), separate syringes and needles being used for each blood sample. Venepuncture was carried out as carefully as possible to reduce tissue trauma to a minimum, and a note was made if any difficulty was encountered in entering a vein. 4·5 ml. of blood was withdrawn and added to a tube containing 0·5 ml. 1·34% sodium-oxalate solution. The tube was inverted two or three times to ensure mixing and was then spun for 5 minutes at 2000 r.p.m. The recalcified-plasma clotting (R.P.C.) time was estimated by adding 0·2 ml. *M*/50 calcium chloride solution to 0·2 ml. of plasma in a glass tube (3 in. x 3/8 in.) in a water-bath at 37°C. The tube was gently tilted at intervals, and the end-point was taken as the first definite appearance of fibrin threads. All estimations were made in duplicate. All the steps in this technique were undertaken by one of us (G. A. M.), and the interval between withdrawal of blood and estimation of R.P.C. time varied very little and was approximately half an hour.

The method was found to give very consistent results. The difference between duplicate readings in no instance exceeded 7 seconds, and averaged 2·2 seconds. As a further check on the reliability of the technique, blood samples were obtained from veins at both elbows at the same time in 19 subjects. Table I shows the results in 15 patients in whom no difficulty in venepuncture was encountered. With 1 exception (case 1) the greatest difference between the two arms was 6 seconds. In the other 4 subjects (see table II) difficulty in venepuncture at one elbow was unavoidable in the first two instances. The R.P.C. times on that side were 28 and 14 seconds less than on

TABLE II—SIMULTANEOUS R.P.C. TIMES (SEC.) IN BOTH ARMS (VENEPUNCTURE DIFFICULT IN RT. ARM)

Rt. arm	Lt. arm	Difference
75	103	28
110	124	14
115	130	15
73	87	14
		Mean 17·8

the other. In the remaining 2 subjects venepuncture at the right elbow was deliberately preceded by slight tissue trauma by the entering needle. The R.P.C. times on that side were 15 and 14 seconds less than on the other.

The R.P.C. time was used as an index of blood coagulability in preference to the "accelerated clotting-time" using Russell-viper venom and the clotting-time of whole blood in silicone-coated tubes. It has the advantage that no foreign thromboplastin is added as in the venom test, and the technique is simpler than the use of silicone-coated tubes. We have, however, found that all three methods show an acceleration of clotting during the phase of lipæmia after ingestion of a high-fat meal.

Convalescent-ward patients, aged 20–61, with no history of cardiac disability, were selected as subjects. After a sample of venous blood had been obtained from the subjects in the fasting state, they ate one of the following meals:

1. *Animal-fat breakfast.*—2 eggs, 2½ oz. bacon, 1–1½ oz. butter, bread, and tea with milk and sugar. Fat content approximately 85 g.

2. *Vegetable-fat breakfast.*—2 fishcakes fried in margarine; toast with margarine; 1 oz. walnuts (in shells); tea with milk and sugar. Fat content approximately 83 g. (walnuts 14·6 g.; margarine 68·7 g.).

The margarine used in the earlier experiments contained a small amount of hydrogenated marine oil in addition to palm-kernel oil, palm-oil, and groundnut oil. In later experiments we used a margarine made specially for us which contained only coconut oil and groundnut oil. No significant difference in the results was noted when the type of margarine was changed. The addition of walnuts to the vegetable-fat meal was made at the suggestion of the dietitian who prepared it; she felt that patients would have had difficulty in consuming it if the total fat content had consisted of margarine.

Blood samples were obtained at 3 and 4 hours after ingestion of the meal.

Results

Table III summarises the results in 11 subjects who on one day took the high-fat meal containing bacon, butter, and eggs, and on another day the meal high in vegetable fat. In general there is little difference between the readings at 3 and 4 hours. In all 11 subjects the animal-fat meal was followed by significant shortening of the R.P.C. time; at 3 hours this reduction varied from 28 to 66 seconds with a mean of 38·7 seconds; at 4 hours the range was from 24 to 73 seconds with a mean of 35·5 seconds. No difficulty in venepuncture was encountered in this series of experiments.

TABLE III—R.P.C. TIMES (SEC.) BEFORE AND AFTER HIGH-FAT MEALS

Subject	Animal fat			Vegetable fat		
	Fasting	3 hr.	4 hr.	Fasting	3 hr.	4 hr.
1	121	76	84	119	85	94
2	114	86	82	121	77	84
3	132	99	96	138	102	101
4	116	68	74	139	87	83
5	96	65	64	100	95	98
6	109	80	77	101	88	99
7	105	75	76	105	82	86
8	122	74	98	119	84	100
9	103	70	76	113	72	88
10	126	60	53	119	62	50
11	111	76	85	120	68	84
Means	114	75	79	118	82	88

After ingestion of the vegetable-fat meal, no significant shortening occurred in 1 subject (5); in this case difficulty was experienced in entering veins, and this may explain the unexpected result. The reduction in another subject (6) was of doubtful significance (13 seconds) at 3 hours, and only 2 seconds at 4 hours, and there is no obvious explanation for this result. In the other 9 subjects the reductions in the R.P.C. times were of the same order as those found after the high animal-fat meal; at 3 hours the range was from 23 to 57 seconds (mean 41·6 seconds), and for all 11 subjects the mean reduction was 35·6 seconds; at 4 hours the range was 19–69 seconds (mean 35·9 seconds), with a mean reduction for all 11 subjects of 29·7 seconds.

TABLE IV—R.P.C. TIMES (SEC.) BEFORE AND AFTER 50 G. AND 30 G. VEGETABLE FAT

Subject	50 g.			30 g.		
	Fasting	3 hr.	4 hr.	Fasting	3 hr.	4 hr.
1	111	65	79	101	94	87
2	92	63	79	95	89	81
3	81	60	72	78	64	61
4	96	75	67	87	66	53
5	85	75	82	95	77	69
6	130	109	124	133	124	129
7	129	111	125	131	123	129
8	129	118	117	136	129	131
9	139	119	119	146	131	134
10	130	114	100	141	130	118
Means	112·2	90·9	96·4	114·3	102·7	99·2

These observations have been extended by measuring the R.P.C. times in the fasting state and at 3 and 4 hours after 50 g. and 30 g. vegetable fat in 10 additional subjects. The findings are presented in table IV. In this series of experiments the special margarine referred to above (coconut oil and groundnut oil) was the only fat given. At 3 hours after 50 g. vegetable fat the reductions in R.P.C. times varied from 10 to 46 seconds with a mean of 21·3 seconds, and at 4 hours the shortening of the R.P.C. times showed a range of 3 to 32 seconds with a mean of 15·8 seconds. When the fat intake was 30 g. the mean reduction of R.P.C. times was 11·6 seconds (range 6–21 seconds) at 3 hours and 15·1 seconds (range 2–34 seconds) at 4 hours. Accordingly the reductions in R.P.C. times at 3 hours after the ingestion of vegetable fat are proportional to the amount ingested (intake 83 g., mean reduction 35·6 seconds; intake 50 g., mean reduction 21·3 seconds; intake 30 g., mean reduction 11·6 seconds); at 4 hours the difference between 50 and 30 g. of fat is not significant.

Discussion

The results demonstrate clearly that the R.P.C. time shows a similar reduction after the ingestion of animal and vegetable fat when the amount ingested is approximately 85 g. When the intake of vegetable fat is reduced the shortening of the R.P.C. time is less pronounced. In view of the discrepancies in the results of other workers we have paid particular attention to technique; and we are satisfied that, in our hands, the R.P.C. test gives accurate and reproducible results if no difficulty in venepuncture is encountered. We have been unable to discover a satisfactory explanation for the failure of some workers to find a shortening after the ingestion of vegetable fat.

It seems reasonable to suggest that, since alimentary lipæmia accelerates the clotting of blood in vitro, it may lead to increased fibrin formation in vivo and so initiate and accelerate the development of atherosclerosis. Our results show that, if this hypothesis is correct, animal and vegetable fats of the types used in our experiments are likely to have the same influence on the development of this process.

Summary

The clotting-time of recalcified plasma is a satisfactory measure of the increase in coagulability following a high-fat meal if there is no difficulty in venepuncture.

Equal amounts of the animal and vegetable fats used in our experiments produced approximately the same increase in coagulability.

References overleaf

EFFECT OF PHYSICAL ACTIVITY ON INCREASED COAGULABILITY OF BLOOD AFTER INGESTION OF HIGH-FAT MEAL

G. A. McDONALD
M.B. Aberd.
LECTURER IN MEDICINE

H. W. FULLERTON
M.D. Aberd., F.R.C.P.
REGIUS PROFESSOR OF MEDICINE
UNIVERSITY OF ABERDEEN

PREVIOUSLY we have adduced evidence which suggests that *one* factor which has a causal relationship to the increasing incidence of coronary atheroma and cardiac infarction may be the increase in dietary fat which has occurred over the past few decades (Fullerton et al. 1953, Fullerton 1955, 1956). More recently we have shown that blood coagulability, measured by the recalcified plasma-clotting time (R.P.C.), increases in approximately equal degree after the ingestion of animal fat (bacon, butter, and eggs) and vegetable fat (mainly margarine) (McDonald and Fullerton 1958). As Morris (1957) has pointed out, the increasing mortality from coronary-artery heart-disease has followed changes in vegetable-fat intake more closely than the alteration in animal-fat consumption, but he has stressed that epidemiological studies have failed to confirm the hypothesis of a single or simple dietary ætiology for ischæmic heart-disease. We have already expressed a similar opinion (Fullerton 1956); and, in our view, attempts to explain the increasing incidence of coronary atheroma and cardiac infarction by reference to the single factor of greater fat consumption have confused the ætiological picture.

Another trend which has been conspicuous in the past few decades has been the general decline of physical activity, largely owing to the increase in mechanisation of industry and in all forms of mechanical transport. Morris et al. (1953) advanced the hypothesis that men in physically active jobs have a lower incidence of coronary-artery heart-disease in middle age than men in physically inactive jobs, and pointed out that the disease is not so severe in physically active workers. Further suggestive evidence has been provided by Brown et al. (1957), who showed that among men in Birmingham aged 60–69 the prevalence of coronary-artery disease seemed to be unrelated to mental activity or smoking habits, but was fairly closely related to the physical demands of occupation, being highest for men in sedentary work. Considerations such as these have prompted us to study the effect of physical activity on the increase in blood coagulability which follows ingestion of a high-fat meal.

Methods

The experiments were carried out in healthy male medical students aged 20–27.

"*Sedentary*" *Day*

On a weekday each student reported at the hospital at 8.30 A.M., where, after a fasting venous-blood sample had been removed, he consumed a breakfast containing approximately 85 g. fat ($2^1/_2$ oz. bacon, 2 eggs, $1–1^1/_2$ oz. butter, bread, and tea with milk and sugar). He reached hospital by private or public transport and the distance which had to be covered by walking did not exceed $^1/_2$ mile. From 9 A.M. onwards he attended lectures and clinical instruction, walking approximately 200–300 yards in the intervals between them. At 12.30 P.M., $3^1/_2$ hours after completion of the breakfast, a second blood sample was obtained.

"*Active*" *Day*

On Saturday mornings the procedure adopted was exactly the same except that no classes were attended and each student observed the following schedule:

8.30–9 A.M.: breakfast (fat content 85 g.).
9–10 A.M.: walking at a moderate pace for 3 miles.
10–10.40 A.M.: rest.
10.40–11.40 A.M.: walking for 3 miles.
11.40–12.30 P.M.: rest.

Blood samples were again obtained before breakfast and $3^1/_2$ hours after it.

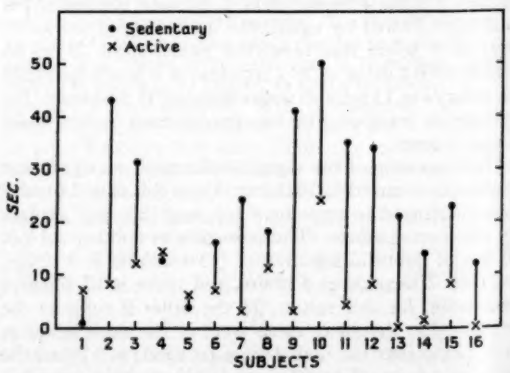
In all cases coagulability was estimated by measuring the recalcified-plasma-clotting (R.P.C.) time by the technique which we have described in a recent communication (McDonald and Fullerton, 1958). An alteration in the R.P.C. time of 12 seconds or more has been regarded as significant.

TABLE I—R.P.C. TIMES (SEC.) FASTING (F) AND $3^1/_2$ HOURS AFTER 85 G. FAT

Subject no.	Sedentary			Active		
	F	$3^1/_2$ hr.	Difference	F	$3^1/_2$ hr.	Difference
1	136	135	1	137	130	7
2	151	108	43	129	121	8
3	140	109	31	133	121	12
4	129	116	13	138	124	14
5	125	121	4	132	126	6
6	123	107	16	143	136	7
7	161	137	24	126	123	3
8	158	140	18	121	110	11
9	133	92	41	108	105	3
10	154	104	50	139	115	24
11	158	123	35	134	130	4
12	152	118	34	146	138	8
13	137	116	21	132	132	0
14	135	121	14	136	135	1
15	147	124	23	143	135	8
16	122	110	12	133	133	0
Means	141·3	117·6	23·8	133·1	125·9	7·3

Results

23 subjects were observed on the "sedentary" day, and 16 of these on the "active" day as well. The results in these 16 subjects are shown in table I and are represented diagrammatically in the accompanying figure. 2 subjects (1 and 5), who showed no significant shortening of the R.P.C. time at $3^1/_2$ hours while "sedentary", are included in this group. Because we were anxious to complete our observations before the start of a student vacation we later decided to observe, during the "active" day, only subjects who showed a significant reduction of



Reductions in R.P.C. times $3^1/_2$ hours after 85 g. fat.

DR. MCDONALD, PROF. FULLERTON : REFERENCES

Biggs, R., Macfarlane, R. G. (1953) Human Blood Coagulation. Oxford.
Fullerton, H. W., Davie, W. J. A., Anastasopoulos, G. (1953) *Brit. med. J.* ii, 250.
— (1955) *Proc. R. Soc. Med.* **48**, 664.
— (1956) *Proc. Nutr. Soc.* **15**, 66.
Keys, A., Buzina, R., Grande, F., Anderson, J. T. (1957) *Circulation*, **15**, 274.
Maclagan, N. F., Billimoria, J. D. (1956) *Lancet*, ii, 235.
O'Brien, J. R. (1956) *ibid.* ii, 232.
— (1958) *ibid.* i, 410.
Pilkington, T. R. E. (1957) *Clin. Sci.* **16**, 261.

TABLE II—R.P.C. TIMES (SEC.) FASTING (F) AND $3^1/_2$ HOURS AFTER 85 G. FAT

Subject	Sedentary		
	F	$3^1/_2$ hr.	Difference
17	146	136	10
18	124	124	0
19	147	140	7
20	139	134	5
21	129	126	3
22	135	123	12
23	132	128	4
Means	136·0	130·1	5·9

R.P.C. time at $3^1/_2$ hours while " sedentary ". The findings in the remaining 7 subjects are shown in table II.

Table I and the figure show that in all the subjects except 2 (1 and 5), the R.P.C. time at $3^1/_2$ hours was significantly shorter (difference 12 seconds or more) than the fasting reading while the subjects were " sedentary ", the mean reduction for all 16 subjects being 23·8 seconds. The results obtained when the subjects undertook the moderate exertion described above were strikingly different. The mean reduction for all 16 subjects at $3^1/_2$ hours was only 7·3 seconds. Omitting subjects 1 and 5, it is seen that the significant shortening (difference 12 seconds or more) at $3^1/_2$ hours in the " sedentary " phase is abolished in eleven subjects (2, 6–9, 11–16) and is much less in 2 (subjects 3 and 10) as a result of the moderate exercise. Subject 4 showed a barely significant reduction at $3^1/_2$ hours, of the same degree during both the " sedentary " and " active " phases. In no instance was the reduction of R.P.C. at $3^1/_2$ hours significantly greater on the " active " day than on the " sedentary " day.

The results obtained in " sedentary " medical students have been significantly different from those found in convalescent ward patients, aged 20–61, with no history of cardiac disability (McDonald and Fullerton 1958). These are presented in table III, arranged in two age-groups—20–24 and 30+. It is seen that: (1) the fasting R.P.C. time in the convalescent-ward patients is significantly lower in both age-groups than in the students; (2) the reductions in R.P.C. time in the convalescent patients are greater for both age-groups than in " sedentary " students; and (3) a significant reduction in R.P.C. time occurred at 3 and 4 hours in all 11 convalescent patients, whereas a significant shortening was found at $3^1/_2$ hours in only 14 of 23 " sedentary " students. It is proposed to extend these observations, but it seems probable that even the small amount of physical activity undertaken by the students on the " sedentary " days may be sufficient to account for the longer fasting R.P.C. time, and the less conspicuous shortening of this time $3^1/_2$ hours after the intake of 85 g. fat. The activity undertaken by convalescent ward patients is, of course, very little and entails walking only a few yards.

TABLE III—CONVALESCENT WARD PATIENTS: R.P.C. TIMES (SEC.) FASTING (F) AND 3 AND 4 HOURS AFTER 85 G. FAT

Age (yr.)	F	3 hr.	Difference	4 hr.	Difference
20	121	76	45	84	37
24	116	68	48	74	42
21	96	65	31	64	32
20	103	70	33	76	27
23	126	60	66	53	73
Means ..	112·4	67·8	44·6	70·2	42·2
33	122	74	48	98	24
36	111	76	35	85	26
49	105	75	30	76	29
50	114	86	28	82	32
58	132	99	33	96	36
61	109	80	29	77	32
Means ..	115·5	81·7	33·8	85·7	29·7

Discussion

The hypothesis that the incidence of coronary-artery disease is inversely related to the general level of physical activity accords well with the findings presented above. If shortening of the R.P.C. time can be regarded as indicating a greater tendency to fibrin formation in vivo, and if intravascular fibrin formation is the important factor leading to atheroma, it follows that any factor which operates over long periods and which can be shown to shorten the R.P.C. time is likely to be causally related to the development of atheroma. In our opinion two of these factors are high intake of fat and low level of physical activity. It is clear that other factors are important in regard to the development of coronary atheroma, as is evident from consideration of the sex distribution and the constitutional predisposition to the development of this lesion; but these cannot be held to account for the increasing incidence. In many respects coronary-artery heart-disease seems to be a penalty which must be paid for a " higher standard of living ". Many changes are involved when this standard is raised, in addition to an increase in dietary fat and a decrease of physical activity; but, since these two changes have been shown to increase blood coagulability, it seems reasonable to regard them as more important than factors of which have not been assessed in this objective manner. If the development of atheroma depends on a long-continued process which favours fibrin formation without a concomitant increase of fibrinolysis, and if physical activity operates in the way we have suggested, it follows that a high general level of activity may well be important in preventing the development of atheroma, whereas phases of much physical activity at long intervals in a sedentary life are unlikely to delay significantly the progress of atheroma. The business executive who undertakes little physical activity throughout the week is unlikely to compensate for this by playing several rounds of golf at the weekend.

One factor in addition to physical activity which varied between the three groups of subjects studied was the degree of mental activity. This could be regarded as moderate in the " sedentary " students, and negligible in students on the " active " day and in the convalescent patients. The reduction in R.P.C. time after the high-fat breakfast was greatest in convalescent patients, intermediate in " sedentary " students, and least in physically active students. In other words it was inversely proportional to physical activity but was not directly correlated with mental activity. It may be that the mental activity of the students on the " sedentary " days was insufficient to produce a distinct effect on coagulability, and further studies under conditions involving different degrees and types of mental activity might be rewarding.

Summary

The acceleration of the recalcified-plasma-clotting (R.P.C.) time after the ingestion of 85 g. fat was, to a large extent, abolished by moderate physical activity.

The fasting R.P.C. time was shorter, and its reduction after 85 g. fat was greater in convalescent-ward patients than in " sedentary " students.

REFERENCES

Brown, R. G., Davidson, L. A. G., McKeown, T., Whitfield, A. G. W. (1957) *Lancet*, ii, 1073.
Fullerton, H. W., Davie, W. J. A., Anastasopoulos, G. (1953) *Brit. med. J.* ii, 250.
— (1955) *Proc. R. Soc. Med.* **48**, 664.
— (1956) *Proc. Nutr. Soc.* **15**, 66.
McDonald, G. A., Fullerton, H. W. (1958) *Lancet*, ii, 598.
Morris, J. N., Heady, J. A., Raffle, P. A. B., Roberts, C. G., Parks, J. W. (1953) *Lancet*, ii, 1053.
— (1957) *ibid.* i, 410.

NEPHROTIC SYNDROME AFTER THE APPLICATION OF MERCURY OINTMENT

N. E. WILLIAMS
M.B. Lpool
LATE HOUSE-PHYSICIAN

H. G. T. BRIDGE
B.M. Oxon., M.R.C.P.
MEDICAL REGISTRAR

CLATTERBRIDGE GENERAL HOSPITAL; WIRRAL, CHESHIRE

FOR many years mercurial salts have had the reputation of being dangerous to nervous and renal tissue. In 1948 Warkany and Hubbard warned against the risk of pink disease when calomel is given for teething troubles: they showed that children with this disease excrete large amounts of mercury in the urine. Bivings and Lewis (1948) confirmed the relationship and reported good response to dimercaprol (BAL) in 1 case. Pink disease, however, may not be the only risk. Wilson et al. (1952) reported 5 cases of renal disease, which may have been caused by calomel; and Farquhar (1953) described an infant who developed pink disease at five months and fatal kidney damage a year later. More recently Stoneman (1958) reported pink disease in siblings following the application of ung. hydrarg. ammon. to the anal margins.

Case-report

A lorry-driver, aged 52, was admitted to hospital in June, 1957, complaining of swelling of his ankles for a fortnight. He had also noticed some breathlessness on effort and mild, gnawing, upper-abdominal pain after meals for a few weeks. For over ten years he had suffered intermittently from psoriasis and he had been advised to rub in an ointment containing 5% ammoniated mercury, 15% tar, and 2% salicylic acid. He had done this very regularly.

On examination he had puffy eyelids and ankle œdema. There was a psoriatic rash on his chest and limbs. His urine contained albumin, 4 g. per 100 ml. There was no other abnormality: his blood-pressure was 140/90 mm. Hg. The serum-cholesterol was 650 mg. per 100 ml., plasma-proteins 3·7 g. per 100 ml. (albumin, 1·3 g., globulin, 2·4 g.), and blood-urea 26 mg. per 100 ml. The serum electrolytes, liver-function tests, chest X-ray, and barium meal were normal.

The diagnosis of nephrotic syndrome was made and the patient was started on a high protein low-salt diet. He was also given repeated double-strength plasma transfusions, acetazolamide, and katonium ion-exchange resin. Despite this, his condition became worse: his œdema rose to his thighs and sacrum, and he developed a small area of consolidation in one lung. In view of this deterioration the diagnosis of mercurial poisoning was considered and the urinary excretion of mercury estimated. This was 240 μg. in twenty-four hours. The patient was then started on a therapeutic trial of dimercaprol and the mercury excretion-test was repeated. The twenty-four hour excretion was 640 μg. on the fourth day of treatment and 1241 μg. on the ninth day. By the eighteenth day it had fallen to 84 μg. From then onwards improvement was maintained. Five months later the patient was completely well and the blood and urine findings were normal. For safety's sake he was given a second course of dimercaprol.

Conclusion

A patient developed a nephrotic-type illness following the application during many years of an ointment which contained ammoniated mercury, tar, and salicylate. The high urinary excretion of mercury and the immediate clinical response to treatment with dimercaprol suggests that the cause of the illness was mercury poisoning. The nervous system was not involved, and the renal changes were reversible.

Because of the wide use of mercury salts the possibility of this complication is worth remembering.

Our thanks are due to Dr. R. R. Hughes, under whose care the patient was treated, and who made the diagnosis. We should also like to thank Dr. H. G. Farquhar for his help and Dr. Hugh McLean, Dr. Eve Patterson, and Mr. R. L. Grainger for the laboratory estimations.

REFERENCES

Bivings, L., Lewis, G. (1948) *J. Pediat.* **32**, 63.
Farquhar, H. G. (1953) *Lancet*, ii, 1186.
Stoneman, M. E. R. (1958) *ibid.* i, 938.
Warkany, J., Hubbard, D. M. (1948) *ibid.* i, 829.
Wilson, V. K., Thomson, M. L., Holzel, A. (1952) *Brit. med. J.* i, 358.

TREATMENT OF INTERMITTENT CLAUDICATION WITH VITAMIN E

PETER D. LIVINGSTONE
M.B. Edin., F.R.C.S.E.
SENIOR REGISTRAR

CLIFFORD JONES
M.B.E., M.B. Lond., F.R.C.S.
CONSULTANT SURGEON

UNITED SHEFFIELD HOSPITALS

OPINION on the value of vitamin E in the treatment of peripheral vascular disease differs widely.

Boyd et al. (1949) reported favourably on its use in a series of 81 patients with intermittent claudication. Boyd classifies these patients into three types: type I are those in whom, on continuing walking or exercise, the pain disappears; type II are those in whom the pain attains a certain level and eventually the patient stops because of persistence of pain; and type III are those who stop because of its increasing severity. He stated that all type-I cases obtained good results with vitamin E; in type II, 27 out of 72 obtained good results, 32 were improved, and 13 were unrelieved; whereas in type III the therapy had no effect. This report, however, is open to criticism as the series did not appear to be adequately controlled.

Baer and Heine (1949) threw doubt on the efficacy of the vitamin; and Hamilton and Wilson (1952) also reported unfavourable results, but in a very small series of cases. Hamilton et al. (1953) later reported a controlled series of 41 cases and expressed the opinion that vitamin E was of no value in the treatment of intermittent claudication. This report has been criticised on the ground that the patients were treated for only twelve weeks.

This discrepancy between different reports encouraged us to carry out a controlled experiment in a series of patients with intermittent claudication.

Material

The series consisted of 40 non-diabetic male patients with obliterative vascular disease who complained of intermittent claudication. Males were selected for the ease of obtaining adequate numbers, as well as to eliminate any possible sex difference in response.

In all cases symptoms had been present for at least five years, and in all cases the pain was felt in the calf muscles. 3 patients had had lumbar sympathectomy without lasting improvement. All had received physiotherapy, and some had had grafts without lasting improvement.

The average age of the control group was 57, and that of the vitamin-E group 55·9. There were 3 patients aged 40–50 in each group.

Following Boyd's grading we found we had no cases of type I. The distribution of the patients is shown in table I.

TABLE I—NUMBER OF CASES OF EACH TYPE

Group	Type I	Type II	Type III
Vitamin E	—	9 (45%)	11 (55%)
Control	—	10 (50%)	10 (50%)

There was a slightly greater proportion of type-III cases in the vitamin-treated group. Too much importance must not be placed on this, however, as in this condition, which must be assessed by symptoms, grading depends very much on the patient's pain threshold and also his cooperation in continuing to walk after the pain has come on. Furthermore, it appeared probable that many patients, because of past experience, stop long before the pain becomes intolerable; therefore stress was not put on this grading.

Method

It was decided to give large doses of vitamin E in tablets. Each tablet was of 200 mg. and the usual daily dose was 600 mg. Each patient was given tablets over a period of forty weeks.

As it was intended to carry out a blind control trial, some "dummy" tablets were made up which were indistinguishable from the vitamin-E tablets. Tablets were put up in identical tubes each containing twenty-one tablets (one week's treatment) and each tube was labelled with a code number. There were forty tubes for each patient, representing forty weeks' treatment. The tubes were sent to the dispensary. As each patient attended his name was entered in a register, and he was given a number which corresponded to the number on the tubes. This ensured that he should have precisely similar tablets throughout the course of the experiment.

The key to the test was not opened until the results had been declared. It was considered that by this method evaluation of the results would be completely unbiased.

Investigation

In addition to a full clinical history, special inquiry was made as to any previous treatment and the results thereof. This was followed by a full general examination, with particular attention to the lower limbs. Bilateral femoral arteriography, carried out in all cases, showed pronounced arteriosclerotic changes and occlusion. Owing to the difficulty in a busy outpatient clinic of keeping a constant-temperature room, and also of keeping a constant room-temperature, it was decided to dispense with skin temperatures.

TABLE II—PATIENTS' OWN ASSESSMENT OF RESULT

Result	Vitamin E	Control
Improved	13	2
No change	4	15
Withdrawn owing to complications of the disease	3	3

In a complaint such as this, where the manifestations are entirely subjective, it is very difficult to measure precisely deterioration or improvement. It was decided that, of all the tests, a simple exercise-tolerance test would give us the best indication. A simple test was selected so that it could be readily understood by the patient, and so that intelligence played no part in the quality of the performance.

The test consisted in climbing up and down a series of two steps 18 inches high, and continuing to do this until pain made the patient stop. The number of steps was counted, and the time of recovery from pain was also noted. One large source of error is the variation in speed at which the patient performs the test; for, if the patient does it rapidly, the number of circuits (climbing up and down the steps) is much reduced. Efforts were made to dispose of this source of error by assessing the time per circuit before the test started; and this was used as the patient's pacemaker for future visits, so that the speed could be kept reasonably uniform.

Results

20 patients were treated with vitamin E and 20 with dummy tablets. We assessed our results in two ways: (1) patient's own assessment, and (2) the improvement in the average number of circuits from the start of the treatment. The results are shown in tables II–IV.

The 13 patients on vitamin E who thought they had improved (table II) also showed objective improvement as shown by the exercise-tolerance test. Of the control group, only 2 showed subjective and objective improvement. 2 patients of the control group said they deteriorated despite the apparent improvement of 5–10 steps. In the vitamin-E group there was a considerably greater increase in the number of circuits achieved by the patients after treatment was completed.

In the vitamin-E group 3 patients had to be withdrawn during the first three months. 1 required amputation for gangrene; another was withdrawn because of incapacity due to a heart lesion; and finally 1 was admitted to hospital with hæmaturia, and did not return to the test. Treatment was also suspended in 3 patients of the control group, of whom 1 died, 1 developed cerebral thrombosis, and 1 was severely handicapped by osteoarthritis of the knees.

TABLE III—AVERAGE NUMBERS OF CIRCUITS AFTER TREATMENT

No. of circuits	Vitamin E	Control
Average before treatment	24	29
Average after treatment	39	31·5
Average increase	15	2·5

17 patients remained in the group treated with vitamin E and, of these, 4 did not respond at all to treatment. Of these 4 failures, 1 had very extensive arterial disease, and both his legs were in great danger of gangrene; 1 was grossly hypertensive; the 3rd was grossly overweight and smoked heavily, and absolutely refused to cooperate in any restrictions of diet or habits; in the 4th patient there was no obvious reason for the failure to respond.

The remaining 13 patients showed much improvement. 7 were able to continue walking indefinitely at a slightly slower pace than usual, and 4 were able to walk any distance of up to half a mile and to do their full work. 2 showed slight, but definite, improvement judged by increase in the number of circuits and steps, and were quite certain that they were more active than they had been and that the pain was less severe.

Of the patients in the control group, only 2 recovered sufficiently to walk a useful distance. 1 of these, for no apparent reason, made a complete and spontaneous recovery after suffering from severe claudication for many years, and the other was a case of bilateral popliteal aneurysm which was included in error. All the others in this group derived no appreciable symptomatic relief.

TABLE IV—INCREASES IN NUMBERS OF CIRCUITS AFTER TREATMENT

Increase in no. of circuits	No. of patients	
	Vitamin E	Control
0–5	2	0
6–10	1	3
10+	10	1

Discussion

Any trial such as this is beset by many difficulties and possible sources of error. Although we adopted the Boyd grading, in order to make some sort of classification, it seemed to us open to considerable criticism owing to the different reactions of patients to pain. The time taken for pain to pass off varied widely in successive records, and this time was of little value in assessing our final results. For example, several of the patients with poor exercise tolerance recovered remarkably quickly, and it can only be assumed that these patients anticipated the onset of pain and stopped before it became severe. There was little difference between the ages of patients in the two groups, and each group included 3 cases of the younger age-groups.

The average increase of 15 circuits in the group receiving vitamin E, compared with 2·5 in the control group, represents a considerable difference, which contrasts with the very slight increase noted by Hamilton et al. (1953). These patients, of course, would show a much greater improvement when walking on level ground.

As would be expected, cases of proximal thrombosis with a good collateral circulation benefited more than cases with extensive obliterative changes—although 2 cases of proximal thrombosis were included in our failures. There was no significant improvement in the nutrition of the skin in any case.

Six months after the end of the trial, of the treated patients who had improved none had deteriorated; and 3 patients in the control group who had been transferred to vitamin E at the end of the trial reported some improvement.

Conclusion

Many criticisms can be applied to this study, but certain simple facts seem to emerge. 13 of a final series of 17 patients on vitamin E improved, where as only 2 of a control group of 17 showed improvement. In successful cases the patients are now carrying on their work with ease, and enjoying their leisure. Apparently vitamin-E therapy does confer benefit in some cases.

All these patients had undergone certain forms of therapy before undergoing this test, and had been disappointed with the results. The fact that improvement was observed in most patients only after some months makes it unlikely that psychological factors played a part.

It is well known that intermittent claudication will sometimes improve without any sort of treatment (Hamilton and Wilson 1952), but in our patients this explanation is unlikely because of the duration of their symptoms.

We were unable to form any criteria which would enable us to select cases which would respond to vitamin-E therapy. We confirmed Boyd's observations that large doses are necessary, and that treatment must be continued for a considerable period. We also found that there is considerable delay before any response can be noted, and we concluded that therapy should be continued for at least three months before being abandoned.

We owe a debt of gratitude to Roche Products for their help and cooperation throughout the trial, and particularly to Dr. Margaret Briggs, their medical director.

REFERENCES

Boyd, A. M., Ratcliffe, A. H., Jepson, R. P., James, C. W. H. (1949) *J. Bone Jt Surg.* **31B**, 325.
Baer, G. A., Heine, W. I. (1949) *J. Amer. med. Ass.* **139**, 733.
Hamilton, M., Wilson, G. M. (1952) *Quart. J. Med.* **21**, 169.
— — Armitage, P., Boyd, J. T. (1953) *Lancet*, i, 367.

CORTISONE AS COVER FOR MAJOR SURGERY IN ADVANCED PULMONARY TUBERCULOSIS

J. R. EDGE
M.D. Leeds, M.R.C.P.
PHYSICIAN, HIGH CARLEY HOSPITAL, ULVERSTON

PATIENTS who had collapsed with peripheral circulatory failure after major operations for advanced pulmonary tuberculosis were observed by me to improve remarkably after administration of cortisone (Edge 1956). There were no untoward effects on the residual tuberculous disease, and I suggested that such patients were suffering from adrenocortical deficiency.

The present paper describes 17 patients with advanced pulmonary tuberculosis for whom major surgery was considered to offer the only real hope of permanently arresting the disease. Each was a very poor surgical risk owing to the bad general condition, and the twenty-four-hour urinary 17-ketosteroid output before operation was found to be low in each case. Replacement steroid therapy was given before, during, and after operation, in order to anticipate possible operative or postoperative collapse.

Clinical Material

There were 17 patients (14 male, 3 female), whose ages ranged from 26 to 58 (mean 45). The operations carried out were pneumonectomy in 5, lobectomy in 4, local excision of cavity in 1, and thoracoplasty in 7. The patients have been followed up for from six to twenty-one months after operation.

Extent of Disease

Chest radiography showed the number of zones involved to range from 3 to 6 (mean 5·1); the total cavity diameter ranged from 4 to 12 cm. (mean 6·8 cm.).

Sputum Status

The sputum of all 17 patients on admission to hospital contained tubercle bacilli on smear, and 12 remained sputum-positive up to the time of operation. The remaining 5 became sputum-negative between two and four months before operation. A significant level of bacterial resistance was demonstrated in 10 patients; in 3 the organisms were shown to be fully sensitive; whilst in 4 no information is available.

Urinary Excretion of 17-Ketosteroids

Twenty-four-hour urinary excretion of 17-ketosteroids was measured by the modified Callow-Zimmerman technique (Dyke 1951). In the 3 women excretion ranged from 1·5 to 4·2 mg. per twenty-four hours (mean 3·2 mg.) (mean normal value in females, 9 mg. per twenty-four hours); and in the 14 men from 2·8 to 8·9 mg. per twenty-four hours (mean 6·7 mg.) (mean normal value in males, 15 mg.).

The twenty-four-hour 17-ketosteroid excretion was also measured in 10 men (aged 24–58, mean 41) all of whom had pulmonary tuberculosis of more limited extent, which was responding satisfactorily to antibacterial treatment alone, and all of whom were in very good general condition. In these patients the values were higher than in those with advanced disease, ranging from 8·8 to 18·0 mg. daily (mean 13·0 mg.). These figures correspond with those cited by Dyke (9–23 mg. [mean 15 mg.] per twenty-four hours) as normal for males.

Replacement Cortisone

When the resting urinary twenty-four-hour 17-ketosteroid excretion was found to be low, cortisone by mouth was started three days before operation in a daily dosage of 100 mg. (25 mg. six-hourly); this was continued for a week after operation, and then reduced in weekly steps of 25 mg. to 75, 50, and 25 mg. daily. The total duration of treatment was four weeks.

Postoperative Course

Mortality

There were three postoperative deaths. 1 patient died a week after operation from uræmia due to renal amyloid disease; the 2nd died suddenly, on the third day after pneumonectomy, from spontaneous pneumothorax on the good side; and the 3rd, who carried organisms highly resistant to streptomycin, isoniazid, and *p*-aminosalicylic acid, died of bronchopleural fistula ten weeks after operation.

Complications

The remaining 14 had no postoperative complications, apart from transient basal collapse in 1 instance. The postoperative course was remarkably free of incident; the patients remained free of fever, dyspnœa, hypotension, and tachycardia and on the day after operation looked and felt none the worse for the operation. The pink colour and lack of any suggestion of dehydration were particularly striking. Wound healing proceeded quite normally in all cases.

Late Results

2 patients have a persistent cavity with consistently positive sputum at nine and twelve months after thoracoplasty, 1 showing total and one partial bacterial resistance. 2 patients remained culture-positive for three and six months after thoracoplasty, but have been since negative up to fifteen and twenty months respectively. The other 10 patients, followed for from six to twenty-one months after operation, have remained radiographically and clinically satisfactory with consistently negative sputum on smear and culture.

Discussion

Steroid hormones have been shown to be of value in the preparation and management of patients undergoing major surgery, apparently acting in one of three ways: (1) by replacing a known deficiency of endogenous steroids in conditions such as Addison's disease and pituitary failure (Troen and Rynearson 1956); (2) by correcting a presumed adrenocortical deficiency in malignant and other wasting diseases (Ruddell and McKeown 1956, Szilagyi et al. 1952, Cole et al. 1953); or (3) by suppressing the disease process in conditions such as ulcerative colitis and hæmolytic anæmia, thus affording an opportunity for surgical treatment (Abbott et al. 1955).

It has been shown by Forbes et al. (1947) that patients with various chronic debilitating diseases (though not including tuberculosis) commonly have a low excretion of 17-ketosteroids in the urine; these patients do not respond to medical or surgical insults by an increase in steroid output, as do normal people (Sandberg et al. 1954). In corollary, several workers have pointed out the greatly increased risk of surgery in patients whose adrenal function had been suppressed by steroid therapy, and in whom replacement had not been continued over the operative period (Hayes 1956, Allanby 1957, Slaney and Brooke 1957); while Popert and Davis (1958) found no increased liability to postoperative complications in a group of patients whose long-term steroid treatment was continued over the operative period.

Earlier fears of activating any tuberculous infection present appear to be ill founded, provided adequate antibacterial treatment is also given (Houghton 1954). In the present series the giving of cortisone for four weeks to 10 patients with resistant organisms was followed by bronchopleural fistula in only 1 instance; this might have been expected in any case in view of the high level of resistance present.

With the increasing use of long-term chemotherapy, major surgery for pulmonary tuberculosis is being increasingly reserved for patients with far-advanced disease in whom chemotherapy alone is inadequate. Many such patients present a formidable, and sometimes prohibitive, surgical risk.

The operative mortality (18%) in the present series was certainly no higher than might have been expected bearing in mind the nature of the clinical material; in each case death was directly due to a definitive complication unrelated to stress. The equanimity with which the remaining patients tolerated the stress of operation was remarkable.

The present study suggests that it would be useful further to investigate adrenal function in patients debilitated by tuberculosis or other chronic illness who require major surgery, with a view to replacing adrenal steroids where these are found to be deficient.

Summary

17 patients with far-advanced pulmonary tuberculosis, in very poor general condition, were submitted to major surgery. Each had a low twenty-four-hour urinary 17-ketosteroid excretion before operation, and the operative period was covered by oral administration of cortisone.

There were 3 postoperative deaths from definitive complications unrelated to stress. The remaining patients tolerated operation well. It is suggested that the replacement of deficient endogenous adrenal secretion contributed substantially to their recovery.

My thanks are due to Mr. J. S. Glennie and Mr. P. Jewsbury, who operated on the patients; and to Dr. J. E. Horrocks and his staff who carried out the urinary 17-ketosteroid estimations. The expenses of this work were defrayed by a grant from the Research subcommittee of the Manchester Regional Hospital Board.

REFERENCES

Abbott, W. E., Kreiger, H., Levey, S. (1955) *Ann. intern. Med.* **43**, 702.
Allanby, K. D. (1957) *Lancet*, i, 1104.
Cole, W. H., Grove, W. J., Montgomery, M. M. (1953) *Ann. Surg.* **137**, 718.
Dyke, S. C. (1951) Recent Advances in Clinical Pathology; p. 222. London.
Edge, J. R. (1956) *Tubercle*, **37**, 166.
Forbes, A. P., Donaldson, E. C., Reifenstein, E. C., Albright, F. (1947) *J. clin. Endocrin.* **7**, 264.
Hayes, M. A. (1956) *Surgery*, **40**, 945.
Houghton, L. E. (1954) *Lancet*, i, 595.
Popert, A. J., Davis, P. S. (1958) *ibid.* i, 21.
Ruddell, J. S., McKeown, K. C. (1956) *Med. Times*, **84**, 255.
Sandberg, A. A., Eik-Nes, K., Samuels, L. T., Tyler, F. H. (1954) *J. clin. Invest.* **33**, 1509.
Slaney, G., Brooke, B. N. (1957) *Lancet*, i, 1167.
Szilagyi, D. E., Marguild, R. R., Jay, G. D. (1952) *Arch. Surg.* **65**, 21.
Troen, P., Rynearson, E. H. (1956) *Clin. Endocrin. Metab.* **16**, 747.

" . . . the scholar . . . is in duty bound to remain unconvinced except upon the most solid assurances, and no one is a whit the worse for his indecision. Now compare his situation with ours, where sick, frightened folk look to us eagerly for treatment, advice, and reassurance. The scholarly fellow who says: 'It may be so and so, but the evidence is incomplete', has little to offer to the sick in body and mind. . . . We are here in a domain more pristine than that of reason, a territory where symbols possess immense power. Some of us in our modern wisdoms run a danger of losing touch with the fears of our patients. We sneer at their dependence on the bottle of medicine, and say they must be weaned from their fanciful attachment. In situations—and they are frequent—in which we are relatively helpless, the bottle of medicine is often the most potent and most economical psychotherapy. There are signs that some patients are being weaned from the bottle—to what? In place of the simple bottle we have to substitute the hypodermic syringe, the psychotherapist, the X-ray apparatus, the physiotherapy department."—Dr. R. E. HOPE SIMPSON, *J. Coll. gen. Practrs*, August, 1958, p. 225.

URINARY δ-AMINOLÆVULIC ACID AND PORPHOBILINOGEN IN DIFFERENT TYPES OF PORPHYRIA

BIRGITTA HAEGER
M.D. Lund
From the Departments of Clinical Chemistry and Medicine (University of Lund), General Hospital, Malmö, Sweden

DURING attacks of acute intermittent porphyria (A.I.P.) increased amounts of porphobilinogen are regularly excreted in the urine. Waldenström (1937) found that in families with A.I.P. several siblings excreted porphobilinogen in the urine without showing symptoms of porphyria. Such cases were regarded as latent. A few persons who had had attacks of typical acute porphyria did not excrete porphobilinogen in their urine when investigated by the methods then available. The question thus arose whether the presence of some earlier porphyrin-precursor in the urine might not be a more reliable criterion of the porphyria-carrier trait.

Recently Mauzerall and Granick (1956) devised a more sensitive method for quantitative determination of porphobilinogen than that described by Vahlquist (1939). They found that the precursor of porphobilinogen, δ-aminolævulic acid, was also present in large amounts in the urine of 2 patients with acute porphyria; and they devised a method for quantitative determination of this substance. Small amounts of δ-aminolævulic acid (ALA) as well as porphobilinogen (PBG) were found even in normal urine.

Material and Methods

Quantitative determinations by the method of Mauzerall and Granick (1956) were made of δ-aminolævulic acid and porphobilinogen in urine from 50 healthy adults, 50 healthy children (aged from seven months to fourteen years), 34 patients with A.I.P., and 128 of their closest relatives, as well as from 12 patients with porphyria cutanea tarda. It was not always possible to obtain twenty-four-hour samples: therefore the results are given in mg. per 100 ml.

At first determinations of the uro- and copro-porphyrins were made semiquantitatively by the method used by Waldenström (1937). Spectral analyses were made of the acid extracts in a Baly cuvette. The following scale was used:

Thickness of layer—>20 mm. = negative: 20–15 mm. =(+): 15–8 mm. =+: 8–1 mm. =++—<1 mm. =+++.

Later the uroporphyrin was determined quantitatively according to Askevold (1951) and calculated according to Rimington and Sveinsson (1950) with corrected factor according to With (1955). As early as 1939 Waldenström and Vahlquist emphasised, however, that quantitative determination of uroporphyrin in acute porphyria is of little value, since porphobilinogen is readily converted to uroporphyrin.

Coproporphyrin was determined by Askevold's modification (1951) of Fischer's original method, with the exception that the last washing was done with a fresh aqueous 1/200 dilution of a 1% solution of iodide in alcohol according to Schwartz, Zieve, and Watson (1951) with calculation according to Rimington and Sveinsson (1950) and corrected factor according to With (1955).

Results

Normal Values

The values of urinary δ-aminolævulic acid and porphobilinogen in 50 healthy adults and 50 healthy children are given in table I.

To exclude errors due to varying concentrations of urine, in the latter part of the investigation the urinary excretion of δ-aminolævulic acid and porphobilinogen was calculated in relation to the excretion of creatinine. Table II shows the normal values when calculated in this way.

TABLE I—NORMAL URINARY CONTENT OF δ-AMINOLÆVULIC ACID AND PORPHOBILINOGEN

	δ-aminolævulic acid (mg. per 100 ml.)		Porphobilinogen (mg. per 100 ml.)	
Adults	M–0·305	S.D.–0·133	M–0·105	S.D.–0·046
Children below 15 years	M–0·257	S.D.–0·115	M–0·047	S.D.–0·031

TABLE II—NORMAL URINARY CONTENT OF δ-AMINOLÆVULIC ACID AND PORPHOBILINOGEN

	δ-aminolævulic acid (mg. per g. creatinine)		Porphobilinogen (mg. per g. creatinine)	
Adults	M–1·9	S.D.–0·6	M–0·7	S.D.–0·4
Children below 15 years	M–3·7	S.D.–1·4	M–0·6	S.D.–0·3

Normal urinary content of uroporphyrin
Semiquantitative method: negative.
Quantitative method: 0–15 μg. per 1 (25 healthy adults).

Normal urinary content of coproporphyrin
Semiquantitative method: (+).
Quantitative method: 0–175 μg. per 1 (50 healthy adults).

Patients with Acute Intermittent Porphyria and their Relatives

The results of the analyses in the different groups are shown in table III and figs. 1–3.

Of 45 persons in group 3, 10 (22%) had latent porphyria. The siblings examined were from 23 different families with 37 known cases of manifest A.I.P. This brings the frequency of latent and manifest porphyria up to

TABLE III—ACUTE INTERMITTENT PORPHYRIA

Group	No. of cases	Normal excretion of ALA and PBG	Pathological excretion of ALA and PBG	Pathological excretion of ALA only	Pathological excretion of PBG only
1. Acute manifest intermittent porphyria	34	0	29	0	5
2. Offsprings of patients with latent or manifest porphyria:					
<15 years	31	21	1	0	9
>15 years	24	18	1	0	5
3. Siblings of patients with latent or manifest porphyria ..	45	35	7	0	3
4. Nephews and nieces of patients with latent or manifest porphyria:					
<15 years	12	12	0	0	0
>15 years	9	9	0	0	0
5. Apparently healthy parents (but genetically certain carriers of the porphyria trait) of patients with latent or manifest porphyria	7	0	6	0	1
Total	162	95	44	0	23

ALA = δ-aminolævulic acid PBG = porphobilinogen

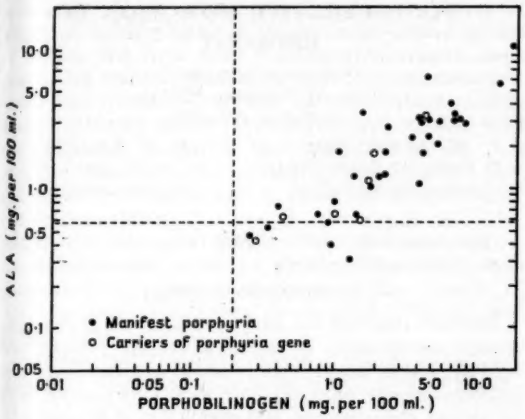


Fig. 1—ALA and porphobilinogen urinary excretion of 34 patients with manifest porphyria and of 7 genetically certain carriers of the porphyria trait. The line parallel to the ordinate corresponds to M+2S.D. mg. porphobilinogen per 100 ml., the line parallel to the abscissa to M+2S.D. mg. ALA per 100 ml. Logarithmic scale.

57%. The value must be somewhat too high; but it does support the widely accepted assumption (Waldenström 1937, 1956 and others) that the trait of A.I.P. is inherited as a simple dominant factor.

If a person's child and one of his parents, or a brother or sister, or a nephew or niece had latent or manifest A.I.P., he was said to be a genetically certain carrier of the porphyria trait. Urine was obtained from 7 subjects satisfying these criteria. These carriers, who had never had symptoms of A.I.P., were between thirty-seven and seventy-one years. In 6 the excretion of δ-aminolævulic acid as well as of porphobilinogen was increased; in the 7th the porphobilinogen only was raised. Thus the values were pathologically increased in all of them (fig. 1). This shows that latent porphyria can remain latent even in the older age-groups. It also suggests that the disease can be transmitted only by persons with latent or manifest A.I.P. This assumption is strengthened by the observations made in group 4, where neither the δ-aminolævulic acid nor the porphobilinogen levels were increased in the urines of offsprings of healthy siblings of patients with A.I.P.

Patients with Porphyria Cutanea Tarda

According to Waldenström (1957) this heterogenous group can be divided into at least two subgroups—porphyria cutanea tarda symptomatica, and porphyria cutanea tarda

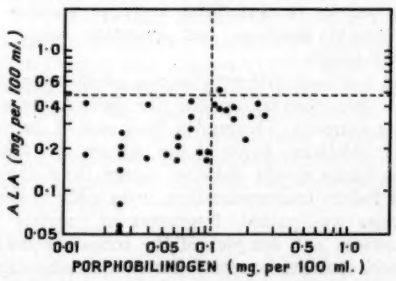


Fig. 2—ALA and porphobilinogen urinary excretion of 31 offspring, below 15 years, of patients with latent or manifest porphyria. The line parallel to the ordinate corresponds to M+2S.D. mg. porphobilinogen per 100 ml., the line parallel to the abscissa to M+2S.D. mg. ALA per 100 ml. (both for children below 15 years). Logarithmic scale.

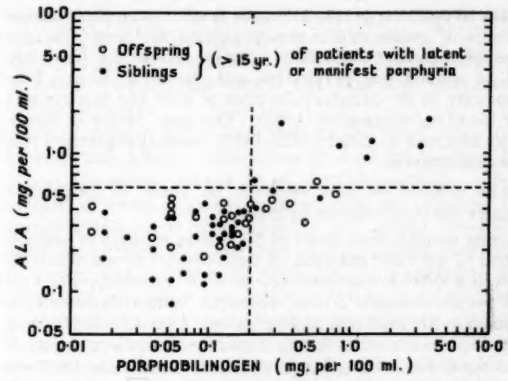


Fig. 3—ALA and porphobilinogen urinary excretion of 24 offspring and 45 siblings of patients with latent or manifest porphyria. The line parallel to the ordinate corresponds to M+2S.D. mg. porphobilinogen per 100 ml.; the line parallel to the abscissa to M+2S.D. mg. ALA per 100 ml. Logarithmic scale.

hereditaria or protocoproporphyria. The classification of most cases is difficult and must be regarded as tentative until further facts are known. It has since been recommended by Rimington (1958).

Porphyria cutanea tarda symptomatica.—This type is mainly characterised by cutaneous symptoms. It usually appears in middle age and has a chronic, benign course. It is often accompanied by liver dysfunction. The excretion of porphobilinogen is usually normal.

Protocoproporphyria.—This type usually becomes manifest around puberty. Here the cutaneous symptoms may be accompanied by colicky pain and rarely by neurological signs. During

TABLE IV—PORPHYRIA CUTANEA TARDA

Case no.	Sex	Age at onset in years	Urine analyses: δ-aminolævulic acid (mg. per 100 ml.)	Porphobilinogen (mg. per 100 m.l)	Uroporphyrin (μg. per l.)	Coproporphyrin (μg per l.)
1. Porphyria cutanea tarda symptomatica						
1	F	16	**1·401** **0·996** 0·287 0·291	0·052 0·090 0·102 0·179	+++ +++ + 11	+ + neg. 108
2	F	72	0·085 0·268	0·102 0·192	+++ **2674**	++ **231**
3	M	35	0·221	0·025	++	(+)
4*	M	42	0·442	0·124	**3145**	**466**
5*	M	54	0·320	0·124	**1360**	**483**
6	M	76	0·136 0·301 0·089	0·014 0·102 0·063	+++ **938** **1903**	+ **378** **228**
2. Protocoproporphyria						
7	F	10 mos.	0·348	**0·140**	**7272**	**895**
8	F	2	0·230	**0·124**	**4040**	**250**
9	F	?	**1·217**	**0·337**	++	
10	F	9	0·202	**0·124**	++	+
11	F	55	0·282 0·056 0·315	0·124 0·025 0·167	**2457** **2069** **1868**	**544** **482** **322**
12	M	45	**0·611** 0·296 0·268	0·077 0·154 0·124	++ **875** **252**	Neg. 105 68

Bold-faced figures exceed M + 2 S.D. for the age-group and are therefore considered pathological.
* Alcoholic.

attacks of colic the porphobilinogen is often increased. Large amounts of proto- and copro-porphyrins are present in the fæces even during remissions. During attacks the fæces are said to contain less porphyrins and the urine more. This reciprocity in the excretory function of liver and kidneys was first noted by Rimington (1952). The large family in South Africa reported by Dean (1953, 1955) certainly represents this type of porphyria.

The results of the analyses in cases of porphyria cutanea tarda are shown in table IV.

Urine samples from some of the closest relatives of patients 11 and 12 were also analysed. A sixteen-year-old son of case 12 showed a slightly increased excretion of δ-aminolævulic acid and porphobilinogen on two occasions without simultaneous increase in the excretion of porphyrins. Two older brothers of case 11, on the other hand, showed a normal excretion of δ-aminolævulic acid and porphobilinogen, while the excretion of porphyrins was increased in both. The proband (case 11) in this family was a fairly heavy drinker; and it is possible that alcohol, by its toxic effect on the liver, unmasked her latent porphyria. It seems quite probable that a genetical defect (a real porphyria) must be present when an alcoholic develops porphyria cutanea tarda.

Summary

Quantitative determinations were made of δ-aminolævulic acid and porphobilinogen in the urine from 34 patients with manifest acute intermittent porphyria, from 128 of their closest relatives, and from 12 patients with porphyria cutanea tarda.

All patients with latent or manifest acute intermittent porphyria showed a pathologically increased excretion of porphobilinogen in the urine. This therefore appears to be an obligatory diagnostic sign. In two-thirds of the patients the excretion of δ-aminolævulic acid was also increased.

In all apparently healthy but genetically certain carriers of the disease the urinary excretion of porphobilinogen, and usually of δ-aminolævulic acid as well, was increased. This suggests that the disease can be transmitted only by persons with latent or manifest porphyria.

A third of the apparently healthy children, below 15 years, of patients with latent or manifest acute intermittent porphyria had biochemical disorders suggestive of porphyria. It is noteworthy that so many of these children had latent porphyria, since manifest porphyria is very rare in this age-group.

In patients with porphyria cutanea tarda the urinary excretion of δ-aminolævulic acid and of porphobilinogen followed no regular pattern. Determination of the porphyrin content of the urine and fæces thus appears more useful in the biochemical diagnosis of this type of porphyria.

The investigation was supported by grants from the Medical Faculty of the University of Lund.

I wish to thank Prof. A. Querido of Leiden, Holland, and Dr. G. Dean of Port Elizabeth, South Africa, for contributing urine samples from patients 7, 8, and 9.

REFERENCES

Askevold, R. (1951) *Scand. J. clin. lab. Invest.* **3**, 318.
Brunsting, L. A. (1954) *Arch. Derm. Syph.* **70**, 551.
Dean, G. (1953) *Brit. med. J.* ii, 1291.
— Barnes, H. D. (1955) *ibid.* ii, 89.
Mauzerall, D., Granick, S. (1956) *J. biol. Chem.* **219**, 435.
Rimington, C., Sveinsson, S. L. (1950) *Scand. J. clin. Lab. Invest.* **2**, 209.
— (1952) *Acta med. scand.* **143**, 161.
— (1958) *Brit. med. J.* i, 640.
Schwartz, S., Zieve, L., Watson, C. J. (1951) *J. Lab. clin. Med.* **37**, 843.
Vahlquist, B. (1939) *Hoppe-Seyl. Z.* **259**, 213.
Waldenström, J. (1937) *Acta med. scand.* suppl. 82.
— Vahlquist, B. (1939) *Hoppe. Seyl. Z.* **260**,189.
— (1956) *Acta genet.* **6**, 122.
— (1957) *Amer. J. Med.* **22**, 758.
With, T. K. (1955) *Scand. J. clin. Lab. Invest.* **7**, 193.

POSTOPERATIVE INFECTION IN UROLOGY

ASHTON MILLER
M.A., M.D. Cantab., F.R.C.S.
CONSULTANT UROLOGIST

W. A. GILLESPIE
M.D. Dubl., F.R.C.P.I., D.P.H.
CLINICAL BACTERIOLOGIST

K. B. LINTON
B.Sc. Brist.
BACTERIOLOGIST

N. SLADE
M.B. Brist., F.R.C.S.
SENIOR UROLOGICAL REGISTRAR

J. P. MITCHELL
M.S. Lond., F.R.C.S., F.R.C.S.E
CONSULTANT UROLOGIST

UNITED BRISTOL HOSPITALS

URINARY infection has long been accepted as the commonest complication of operation on the prostate and bladder, and in fact is often regarded as a necessary evil. Infection mostly produces only local inflammation with no serious consequences, and eventually, if all goes well, it dies out some months after the patient has left hospital. Occasionally it may lead to serious and sometimes fatal results by way of secondary hæmorrhage, pyelonephritis, and septicæmia. It is therefore obvious that, if these occasional serious consequences are to be avoided, great efforts must be made to maintain sterility of the urine after all urological operations.

In the work described here, which has occupied three years, we have had two main objects: to investigate the origin and clinical effects of postoperative infection of the urinary tract and blood-stream, and to find means of preventing infection.

Methods

Except for some of the patients in whom the clinical effects of infection are described, only those whose urine was sterile before operation are included in this report. Of 161 such patients 41 had retropubic prostatectomy and 120 had transurethral operations on the prostate or the bladder. They were admitted to four general surgical wards under the care of two surgeons whose technique did not change significantly throughout the investigation. Antibiotics and sulphonamides were not given before operation and were only used when the clinical condition of the patient was thought to make them necessary after operation. Preoperative drainage was not used, and at operation a plastic or a latex-rubber catheter was placed in the urethra and left in for three days. At first open drainage was used. A sterile rubber tube connected to the catheter hung over the edge of the bed and drained into a pail on the floor. When clots caused obstruction they were either washed out with sterile saline solution or removed by suction from a sterile bladder syringe. Later, closed drainage and irrigation were used, as described below.

Urine was collected with aseptic precautions by one of us each day, starting on the day before operation and omitting Sundays. During the later part of the investigation the following material for culture was taken from patients while in the theatre: swabs from the anterior urethra before instrumentation, urine collected when the cystoscope was passed, fragments of prostate removed by resection, and samples of the irrigating fluid. After operation, specimens were collected either by disconnecting the catheter from the drainage tube or, when patients were on closed irrigation, with a sterile syringe attached to a needle inserted into the wall of the tube, previously swabbed with tincture of iodine. Preliminary tests showed that neither procedure caused contamination of the

specimens. Urine was examined within two hours of collection by microscopy of wet and gram-stained smears of deposit and by a roughly quantitative cultural technique. Six standard loopfuls ($^1/_{150}$ ml.) of uncentrifuged urine were placed side by side on well-dried blood-agar and MacConkey plates. One loopful was streaked over the remaining surface of each plate, which was then incubated as soon as the other loopfuls had soaked into the medium. Colonies were counted and identified after twenty-four hours.

The sensitivity of all the bacteria to antibiotics and the biochemical activities of the gram-negative bacilli were determined by standard methods. Most strains of *Staphylococcus aureus* were phage-typed (Williams and Rippon 1952).

A patient was considered to have developed an infection only if his urine contained at least 3000 bacteria per ml. on two or more consecutive days. This high limit was chosen to eliminate slight or doubtful infections. When an organism appeared first in small numbers and later became numerous, the infection was counted as starting on the day of its first appearance. Infections by coagulase-negative staphylococci (*Staph. albus*) were not included, because the clinical significance of this organism was often doubtful. It was often found in the urethra and, in small numbers, in otherwise normal urine. Though its presence in larger numbers was in some cases accompanied by pyuria, in others there was no evidence of inflammation.

Results

Bacteriology of Urine

Between April 4, 1955, and July 25, 1956, before additional measures were taken to prevent infection, 13 of the 16 retropubic prostatectomies and 29 of the 41 transurethral operations were followed by infection, an overall incidence of 74%. The incidence of infection was much higher than was indicated by the clinical signs and symptoms and higher than would have been detected if only one or two random postoperative samples of urine had been examined from each patient, because some infections cleared in a few days. The bacteria, in order of frequency, were coliform bacilli, proteus, *Staph. albus*, *Streptococcus fæcalis*, *Staph. aureus*, and *Pseudomonas pyocyanea*, but in many cases the infections were mixed. As we reported previously (Gillespie 1956), many of the bacteria originated in the hospital, as was shown by their abnormal resistance to antibiotics and, in the case of staphylococci, by their phage patterns. That cross-infection is often responsible for postoperative urinary infection has been shown by several workers (Ørskov 1952, 1954, Kass 1955, Goldie 1956, Dutton and Ralston 1957). The organisms do not usually come from the patient's own bowel. Gillespie (1956) and Dutton and Ralston (1957) failed to isolate antibiotic-resistant coliform bacilli from the fæces of patients in whom they caused urinary infection.

All the patients with infections had numerous pus cells in their urine, but bacteria often appeared a day or two before the pus. Pus cells were rarely numerous in the absence of infection.

Clinical Effects

Pyrexia higher than 100°F on one or more days of the postoperative period was recorded in 48% of 155 patients chosen at random. Of the patients who remained without postoperative infection, and whose records showed such pyrexia, 82% were affected in this way only on the first or the second postoperative day. Considering, therefore, records of pyrexia from the third day onwards, we found that only 5 of 79 (6%) of patients who remained uninfected showed pyrexia, whereas 42 of 76 (55%) of patients with infection had pyrexia which was probably attributable to the infection.

The duration of the infection varied from a few days to more than a year. Many patients were followed up, but it was impossible to see all at regular intervals. About a third of those who left hospital with an infection had sterile urine after three months, and about two-thirds after six months. A few were still infected a year later. It seems that infection usually clears up spontaneously when the operation site heals and treatment with sulphonamides or antibiotics is often unnecessary. If used, these drugs usually do not influence the ultimate disappearance of the organisms, whose persistence for a long period often indicates a structural abnormality of the urinary tract.

In a few patients infection had serious consequences, with the development of pyelonephritis. In others, not included in this series, we have, during the past two years, seen 1 proved case of subacute bacterial endocarditis and 9 of septicæmia complicating postoperative urinary infection. In 5 cases, 2 of which were fatal, the septicæmia was a complication of an established pyelonephritis and caused deterioration in the condition of an already ill patient. In the 4 others, the picture was more dramatic, with sudden collapse of a previously fit patient owing to a profound fall in blood-pressure, but combined with a rise of temperature; 1 of these patients died, and the 3 others recovered after prompt energetic treatment with intravenous antibiotics. This condition of bacteriæmic shock is an important complication of urological infection and urethral instrumentation (Waisbren 1951, Hall and Gold 1955, Spittel et al. 1956, Ezzo and Knight 1957). It may easily be mistaken for massive pulmonary embolism or severe coronary thrombosis if the strange combination of shock and pyrexia is not noticed, and the result is often fatal unless intravenous antibiotics are quickly given. Even at necropsy the real cause of death may not be obvious.

There is often a rise of temperature, and occasionally a rigor, soon after withdrawal of the indwelling catheter, and it seems likely that the disturbance of an infected operation site may sometimes discharge bacteria into the blood-stream. To investigate this possibility, three blood-cultures were made from each of 51 patients, of whom 29 had sterile urine and 22 infected urine at the time of operation. The first sample of blood for culture was taken immediately before withdrawing the catheter the second within five minutes of its removal, and the third about twenty minutes later.

All blood-cultures were negative from 15 patients whose urine remained sterile after operation; but of 14 patients who developed postoperative urinary infection 7 had positive blood-cultures from blood taken within five minutes of withdrawing the catheter, whereas their first and third samples of blood were negative. The results with the patients who came to operation with urine already infected suggested that bacteriæmia was less likely with long-standing infection than with recently acquired infection. In 15 of this group whose urinary flora was unchanged after operation no positive blood-cultures resulted from withdrawing the catheters; but of 7 whose urine after operation contained new varieties of bacteria 2 had positive blood-cultures from blood obtained within five minutes of withdrawal (table 1). Organisms

TABLE I—BLOOD-CULTURES TAKEN FIVE MINUTES AFTER REMOVING THE INDWELLING CATHETER FROM PATIENTS WITH STERILE AND INFECTED URINE

Urine before operation	Urine when catheter removed	No. of patients	Blood-cultures	
			Positive	Negative
Sterile	Sterile	15	0	15
	Infected	14	7	7
Infected	No additional organisms	15	0	15
	Additional organisms acquired	7	2	5
	Total	51	9	42

similar to those causing bacteriæmia were present in the urine of 6 of the patients (Slade 1958).

Evidently, transient bacteriæmia commonly follows the withdrawal of an indwelling catheter from a recently infected urinary tract, and the difference between this bacteriæmia and a septicæmia may be a matter of the number and virulence of the organisms. These results recall those of Scott (1929) and Barrington and Wright (1930), who showed that transient bacteriæmia sometimes results from the passage of sounds used to dilate urethral strictures. Bacteriæmia was also found by these workers when urine was passed for the first time after dilatation.

Sources and Routes of Infection

Culture of prostatic fragments often yielded a few colonies of *Staph. albus* but no other organism. Bacteria similar to those which caused infection were sometimes isolated from the anterior urethra just before operation but not from numerous swabs of theatre personnel, towels, cystoscopes and other equipment, and sterilising and rinsing solutions. On the other hand, it was always easy to find the organisms on ward equipment and furniture. Irrigation of the bladder in the ward has been shown to be an important cause of infection, and improvements in drainage and irrigation methods can reduce its incidence (Pyrah et al. 1955, Gillespie 1956, Goldie 1956). Dutton and Ralston (1957) showed experimentally that bacteria could ascend to the bladder via the drainage tube and indwelling catheter, and we have found that rising air-bubbles can readily carry organisms up the tube. But bacteria must also enter the bladder in other ways, for some patients developed infection even when treated with closed aseptic drainage and no irrigation (Gillespie 1956). We therefore decided to investigate the effects of improving methods of bladder drainage and irrigation and of changing methods of sterilising urethral instruments in the theatre.

PREVENTION OF INFECTION

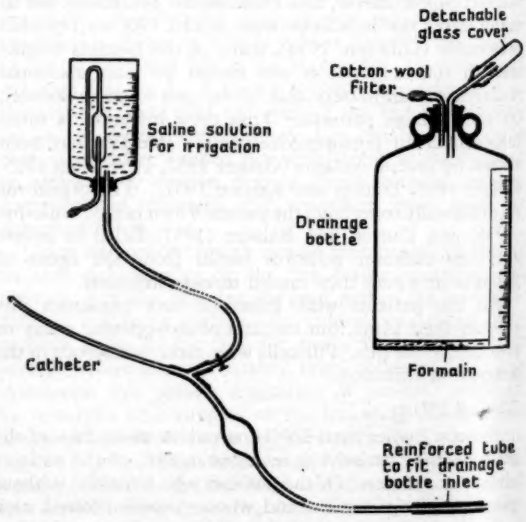
Closed Drainage

The closed-drainage system was set up before the patients left the theatre, by aseptically connecting the indwelling catheter to the sterilised drainage apparatus by means of a 4-ft. length of sterile rubber tubing. The apparatus was prepared beforehand by inserting a rubber stopper fitted with glass inlet and air filter, previously autoclaved, into a 1 gallon 2-handled clear glass bottle (U.G.B.Co., A.L.29), containing 100 ml. of liq. formaldehyde *B.P.C.* The assembled unit was allowed to stand for at least twenty-four hours before use, because tests showed that cultures of *Escherichia coli*, proteus, *Ps. pyocyanea*, and *Staph. aureus*, smeared on the inside of the bottle above the level of the fluid, were killed by exposure overnight to the vapour. In order to allow the contents to be measured for fluid-balance records, volume scales were printed on paper strips which were fixed to the outsides of the bottles (see figure).

In a controlled trial previously reported (Gillespie 1956) we found that the onset of infection was often delayed, but usually not prevented, by the closed aseptic drainage system. Our experience subsequently has been similar. As compared with patients on open drainage, many could be brought through the two or three days of catheter drainage after operation without infection, only to develop an infection soon after the catheter was removed.

Closed Irrigation

An entirely closed method of irrigation was introduced, so that patients whose catheters became blocked by blood-clot after operation could be irrigated with complete aseptic precautions. A 1-litre bottle of sterile saline solution was suspended 1 metre above the bed. The air inlet was fitted with a sterile cotton-wool filter kept dry by means of a non-return fitting. The delivery tube of the saline bottle was connected to a glass Y-piece by means of a rubber tube fitted with a screw clip. The stem of the Y-piece was connected to the indwelling catheter and the other limb to one end of a Higginson syringe from which both valves had been removed. The other end of the syringe was connected to the closed drainage bottle (see figure). The bladder was washed out by allowing saline solution to flow up the catheter by gravity. If clots prevented this, the saline solution was made to flow into the Higginson syringe until it had displaced all air-bubbles there. The supply was then stopped with a screw clip and, pinching the lower tube of the syringe with finger and thumb, the contents of the syringe were forced up the catheter by compressing the bulb with the other hand. When suction was needed to move clots from the catheter, the catheter was pinched by finger and thumb and the bulb emptied into the drainage bottle by compression with the other hand. The lower tube of the syringe was then pinched just beyond the bulb and the catheter released, thus allowing the bulb to expand and producing enough suction to remove all but very big clots from the bladder. These manipulations, although complicated to



Apparatus for closed drainage and irrigation.

TABLE II—INFECTIONS IN RELATION TO METHOD OF WASHING OUT BLADDER

Method	No. of patients	Infected within 18 hr. after operation	"At risk" for infection later	Infection developed during		Total infected
				Remainder of catheter drainage	Subsequently	
Closed irrigation	25	11	14	3	3	17
No irrigation	19	4	15	0	4	8
Total	44	15	29	3	7	25
Open irrigation	19	5	14	8	1	14

describe, proved easy to demonstrate to the nursing staff, who soon learned to perform them correctly. Occasionally, however, this closed method of irrigation failed when bleeding was profuse and clotting pronounced, and the tubing had to be disconnected to allow the use of a sterile bladder syringe. With increasing practice these failures have been limited recently to those cases where neither closed nor bladder-syringe irrigation proved successful, and the catheter had to be changed. Such difficulties, with their consequent risk of infection, could normally be avoided by careful observation of the patient during the early hours after operation. Obstruction to the passage of urine was easy to relieve if dealt with promptly.

The effect of using closed irrigation was tested between Aug. 1, 1956, and Nov. 11, 1957. Some patients, selected at random, had the closed-irrigation apparatus fitted in the theatre. The others also had closed drainage but had wash-outs of sterile saline solution from a sterile syringe when clots had to be removed. The result was a disappointingly small improvement. Infection developed in 25 (57%) of the 44 patients who either had closed irrigation or required no irrigation, compared with 14 (74%) of the 19 with open irrigation. It was seen that the incidence of infection in the immediate postoperative period (up to eighteen hours after operation) was quite unaffected (table II). The reduction in the incidence of infection in the remaining period of catheter drainage was, however, highly significant. On open irrigation, 8 of the 14 patients then "at risk" developed infection before the catheter was removed, whereas with closed or no irrigation, only 3 of 29 patients similarly "at risk" developed infection during drainage (χ^2, corrected for continuity, = 8·5, n = 1, p less than 0·01). Those who had no irrigation of any sort appeared to do best, but the number of patients was too small to be sure of this. Patients who required no irrigation may have been less susceptible to infection. Patients who survived without infection until the catheter was withdrawn often developed persistent infections within twenty-four hours after the withdrawal. The organisms causing these delayed infections did not differ from the others. It seemed that bacteria might persist in the operation site, only to be released and sometimes to cause infection after the disturbance of withdrawing the catheter. If so, the infections which developed after the removal of the catheter, like the immediate postoperative infections, might be attributable to bacteria introduced in the theatre and would reduce the benefit obtained from aseptic drainage and irrigation of the bladder. That this may happen was shown by culturing material adhering to the collapsed bulb of Foley catheters. Of 16 catheters removed from patients whose urine was sterile, 4 yielded heavy growths of bacteria other than *Staph. albus*. Similar organisms were isolated from their urine soon afterwards, but had disappeared by next day and did not cause urinary infection in these particular patients.

Changes in Theatre Technique

A study of our records showed that several patients had developed early postoperative infections by organisms similar to those known to be present in the urine of previous patients on the same operating-list. (Many patients came to operation with urine already infected following previous instrumentation or operation in this or other hospitals.) In 1 instance, the infecting organism was *Staph. aureus* phage-type 77, which had not recently been isolated from the patient's own ward where an investigation of staphylococci was in progress, but was present in the urine of an earlier patient on the same list who came from a different ward. It seemed clear from these findings, and from the constantly high incidence (about 30%) of early postoperative infection despite improved drainage and irrigation that some infections must originate in the theatre by cross-infection within an operating-list. Although swabs taken from time to time from urethral instruments had been sterile, incomplete sterilisation of the instruments was the most likely cause of the cross-infection.

Two changes were therefore introduced: patients with urinary infections were kept, as far as possible, to the end of the operating-list (an obvious precaution which previously had been overlooked), and the method of disinfecting cystoscopes and resectoscopes was altered. Boilable cystoscopes were not available. The instruments in use had previously been disinfected between cases by dismantling, rinsing in running water, and immersing for at least fifteen minutes in 1/2000 mercuric oxycyanide solution contained in shallow dishes. Hayes (1949) showed that oxycyanide was a poor disinfectant—a fact which we have confirmed. Immersion for thirty minutes failed to sterilise strips of metal contaminated with *Staph. aureus*, and proteus and coliform bacilli survived for twenty minutes. Chlorhexidine ('Hibitane') was found to be a much better disinfectant and sterilised large inocula of the same organisms within ten minutes, using a 1/5000 solution in saline. A mixture of hibitane and oxycyanide had a slightly more rapid bactericidal action than hibitane alone. Further studies are being made on the bactericidal action of this mixture. (Media containing sodium thioglycollate, lecithin, and 'Lubrol' were used for bactericidal tests with the disinfectants). Accordingly, we decided to employ an aqueous solution containing 1/5000 hibitane and 1/2000 mercuric oxycyanide for disinfecting cystoscopes and resectoscopes between operations. The instruments were taken apart, washed in running water, and immersed vertically, so

TABLE III—INCIDENCE OF INFECTION WITH "OLD" AND "NEW" ASEPTIC METHODS IN THEATRE (SEE TEXT FOR EXPLANATION)

—	Total patients	Infections				
		Within 18 hr. after operation	In remaining catheter-drainage period	In next 24 hr.	Subsequently	Total
"Old" method (Aug. 1, 1956, to Nov. 10, 1957)	44	15	3	4	3	25
"New" method (Nov. 11, 1957, to March 8, 1958)	30	2	2	3	0	7

All patients had closed or no irrigation and closed drainage.

as to expel air, in tall cylinders containing the disinfectant mixture, for at least twenty minutes. These changes were introduced on Nov. 11, 1957. Of the 30 patients who had operations after this date only 7 (23%) developed infection, compared with 25 (57%) of the 44 previous patients who also had closed irrigation and drainage (table III). The difference was significant ($\chi^2 = 6{\cdot}8$; n = 1; p less than 0·01). Much of the improvement was due to a striking reduction in the incidence of early postoperative infection.

In contrast to the antibiotic-resistant "hospital organisms" which caused many of the infections before Nov. 11, those responsible for all 7 subsequent infections were normally sensitive to antibiotics and may have been derived from the patients themselves. Urethral swabs showed that organisms similar to those which caused 4 of the infections (a coliform bacillus, a streptococcus, and, on 2 occasions, *Ps. pyocyanea*) were present in the anterior urethra before operation, and these may have been carried up by instrumentation.

Since the changes in ward and theatre technique were introduced, there has been a gradual reduction in the infection-rate. The incidence of postoperative infection has fallen from 74% of the 57 patients treated by the old methods, before August, 1956, to 23% of the 30 patients treated since Nov. 11, 1957. The difference is highly significant (χ^2, corrected for continuity = 18·3; n = 1; p less than 0·001). Both types of operation have shared in the improvement; only 2 of the 10 recent retropubic operations and 5 of the 20 recent transurethral operations have been followed by infection.

Discussion

Urinary infection is a very common complication of operation on the prostate and bladder, and is usually the result of cross-infection with antibiotic-resistant organisms derived from the hospital and brought about by instrumentation. Its true incidence may be unsuspected since it often produces little clinical disturbance. Nevertheless it is important to prevent infection, because of its serious results in a minority of patients. It sometimes leads to pyelonephritis, which is probably a blood-borne infection resulting from the transient bacteriæmia that we have detected in many of these patients, and this must be particularly dangerous to a patient with impaired renal function. Bacteria are most likely to enter the blood-stream during the first few days of an infection while the operation site is still unhealed. Their entry may be precipitated by the removal of the indwelling catheter or perhaps by straining at defæcation or micturition. The important complications of bacteriæmic shock, septicæmia, and bacterial endocarditis seem likely to be further extensions of this process.

The changes in our methods of preserving asepsis during and after operation have considerably reduced our infection-rate and have given us the new and welcome experience of performing urological operations and carrying treatment through to its conclusion in a sterile surgical field. The results of culturing preoperative urethral swabs suggest that some infections were caused by bacteria which entered the urethra before operation. McLeod (1958) has demonstrated the importance of this mode of infection. Another possible route of infection is through the secretion which collects between the urethral wall and the indwelling catheter. Although we were previously unable to demonstrate the entry of infecting organisms by this route (Gillespie 1956) the experiments of Kass and Schneiderman (1957) show that it may be important.

Summary

Urological patients with initially sterile urine were studied in general surgical wards for a period of three years.

Postoperative urinary infection was very common, and was usually caused by antibiotic-resistant bacteria endemic in the hospital. Several patients with infected urine suffered transient bacteriæmia when their indwelling catheters were removed. It is suggested that such bacteriæmia may sometimes lead to pyelonephritis, septicæmia, bacteriæmic shock, or endocarditis.

The infection originated sometimes in the theatre and sometimes in the ward. Considerable improvement was achieved by changing the method of disinfecting cystoscopes and resectoscopes and by using of closed aseptic apparatus for draining and irrigating the bladder after operation.

We wish to thank the board of governors of the United Bristol Hospitals for a grant towards the cost of this research, and the ward sisters and Mr. W. Price for their enthusiastic assistance.

REFERENCES

Barrington, F. J. F., Wright, H. D. (1930) *J. Path. Bact.* **33**, 871.
Dutton, A. A. C., Ralston, M. (1957) *Lancet*, i, 115.
Ezzo, J. A., Knight, W. A., Jr. (1957) *Arch. intern. Med.* **99**, 701.
Gillespie, W. A. (1956) *Proc. R. Soc. Med.* **49**, 1045.
Goldie, W. (1956) *ibid*, p. 1047.
Hall, W. H., Gold, D. (1955) *Arch. intern. Med.* **96**, 403.
Hayes, W. (1949) *Brit. J. Urol.* **21**, 198.
Kass, E. H. (1955) *Amer. J. Med.* **18**, 764.
— Schneiderman, L. J. (1957) *New Engl. J. Med.* **256**, 556.
McLeod, J. W. (1958) *Lancet*, i, 394.
Ørskov, I. (1952) *Acta path. microbiol. scand.*suppl. **93**, 259.
— (1954) *ibid.* **35**, 194.
Pyrah, L. N., Goldie, W., Parsons, F. M., Raper, F. P. (1955) *Lancet*, ii, 314.
Scott, W. W. (1929) *J. Urol.* **21**, 527.
Slade, N. (1958) *Proc. R. Soc. Med.* **51**, 331.
Spittel, J. A., Martin, W. J., Nichols, D. R. (1956) *Ann. intern. Med.* **44**, 302.
Waisbren, B. A. (1951) *Arch. intern. Med.* **88**, 467.
Williams, R. E. O., Rippon, J. E. (1952) *J. Hyg., Camb.* **50**, 320.

THE INFLUENCE OF AGE ON EXCRETION OF RADIOACTIVE IODINE

G. A. MACGREGOR *
M.D. Lond., M.R.C.P.
LATE SENIOR MEDICAL REGISTRAR

H. WAGNER
M.D. Johns Hopkins
RESEARCH FELLOW, NATIONAL HEART INSTITUTE, U.S.A.

From the Department of Medicine, Postgraduate Medical School of London, W.12

MEASUREMENT of the urinary excretion of radioactive iodine (^{131}I) has proved valuable in the diagnosis of hyperthyroidism. We suspected, however, that this test was not as reliable in the elderly as it was in younger patients. To see whether the limits of normality varied with age, a group of euthyroid patients of different ages were reviewed.

Material and Methods

In the ^{131}I-excretion test used at this hospital, urine is collected during three periods in the forty-eight hours following the administration of the iodine. The percentage of the dose excreted during the 0–8-hour period, the 8–24-hour period, and the 24–48-hour period is measured, and a thyroid-uptake or "T" index is calculated from the formula $T = \frac{(0\text{–}8)\text{ hours }\% \times 100}{(8\text{–}24)\text{ hours }\% \times (0\text{–}48)\text{ hours }\%}$. This procedure gives results relatively independent of renal function. The currently accepted normal range of the T-index is 2·8—13 (Fraser et al. 1953).

* Now at St. Luke's Hospital, Warren Road, Guildford, Surrey.

In 1952–57 the test was performed on more than 2000 patients. 203 cases (with ages ranging from 20 to 82) were selected from this group. To ensure, as far as possible, that these cases were euthyroid, the following criteria were used. No patients known to have thyroid or renal disease, or in whom the T-index was greater than 13, were included. All cases referred with a provisional diagnosis of hyperthyroidism or myxœdema were likewise excluded, even though the result of the test was within the normal range. The reasons for performing the test in the cases chosen for analysis are shown in table I.

10 of the 213 tests made on these cases were excluded because errors in urine collection were suspected.† The remaining 203 results from 197 patients (147 female and 50 male) were analysed by plotting the T-index, and the excretion values for the individual urine-collection periods against the patient's age.

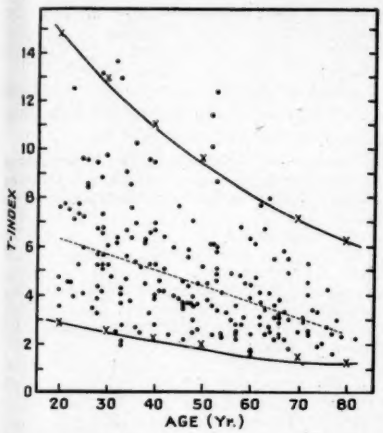


Fig. 1—T-index plotted against age. The equation for the regression (broken) line is T = 7·55 −0·065 age (years). The upper and lower solid lines contain 95% of the points.

Results

In fig. 1 it will be seen that the value of the T-index decreases with advancing age. This is shown by the calculated regression line, which has a slope of −0·065 T-units per year of age ($P < 0.001$). The correlation coefficient of the T-index with age is -0.42 ± 0.07. The distribution of the points suggests that the relationship between the T-index and age may be curvilinear rather than linear. A significant decline is also obtained when log T is plotted against age, and the log T-age regression line was used in calculating the limits of normality shown in fig. 1. 95% of the values lie within these limits.

† In every test the T-index was compared with the 0–48-hour excretion value. The results were outside the range found in 95% of cases, in the 10 rejected tests.

TABLE I—COMPOSITION OF THE GROUP OF PATIENTS WHOSE TESTS WERE COMPARED

Reason for test	Age 20–49		Age 50–82		All ages	
	Tests	Mean T-index	Tests	Mean T-index	Tests	Mean T-index
Before thyroid ablation with ^{131}I for heart disease	23	4·8	25	4·8		
Before hypophysectomy for cancer	3	4·5	22	3·0		
To exclude hyperthyroidism in clinically euthyroid patients with						
(*a*) neurosis	31	5·4	3	4·6		
(*b*) no apparent disease	38	6·5	38	3·6		
Miscellaneous e.g., menstrual disorders	16	4·9	4	4·0		
Total	111	5·6	92	3·8	203	4·8
Selected euthyroid group	47	5·7	19	4·2	66	5·1

This decline in the T-index might be due to lack of uniformity in the composition of the group. Comparison of the diagnoses of the cases above and below 50 years of age shows that there are proportionately more patients with cancer in the older age-group and more cases of neurosis in the younger (table I). However, the decrease is observed even when these cases are discarded. Moreover, analysis of the results obtained in an additional group of 66 subjects selected from hospital personnel and outpatients showed a similar decline in the T-index with advancing age. In this smaller group, chosen as controls because they were clinically euthyroid, the age range was 20–73 years, the slope of the regression line was −0·042 ($P < 0.02$), and the correlation coefficient of the T-index with age was −0·28 ($P < 0.02$).

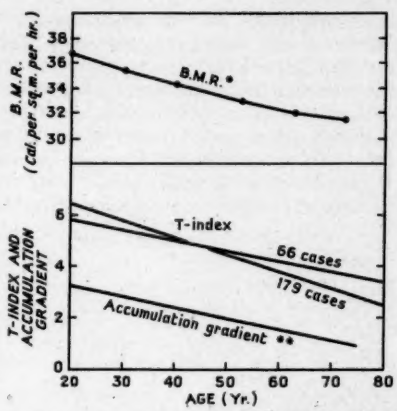


Fig. 2—Comparison of the slopes of the regression lines for the T-index and accumulation gradient. The fall in the basal metabolic rate is also shown (*from Robertson and Reid 1952; **from Perlmutter and Riggs 1949).

The correlation between age and the percentage of ^{131}I excreted during the separate collection periods is shown in table II. Excretion in the first 8-hour period falls with increasing age. The percentage excreted in the 8–24-hour period increases with age, as does that for the entire 48-hour period. The fall in the 0–8-hour value could be due to impairment of renal function through ageing. The increase in the 8–24-hour and 0–48-hour excretion cannot, however, be explained in this way. It is more likely that the increased excretion and the change in the T-index are due to a fall in thyroid uptake.

TABLE II—CORRELATION BETWEEN ^{131}I-EXCRETION AND AGE IN 197 PATIENTS

Urine sample	Correlation coefficient r	Significance P
0–8-hour period	−0·222	<0·01
8–24-hour period	+0·332	<0·001
0–48-hour period	+0·368	<0·001
T-index	−0·420	<0·001

Discussion

A decrease in thyroid uptake with advancing age has been reported in previous ^{131}I studies. Perlmutter and Riggs (1949) found that in a group of 162 euthyroid cases the mean "accumulation gradient", derived from the 1–4-hour neck uptake, fell with each decade from the age of 12 to over 70. Quimby et al. (1950), in a survey of 1050 tests on euthyroid patients, also detected a smaller but statistically significant decrease in the 24-hour thyroid uptake with increasing age. The rate of decline of the accumulation gradient with age observed by Perlmutter and Riggs (1949) closely resembles that of the T-index in our series. Calculated from their data, the slope of the

regression line is −0·048 units per year. The fall in the thyroid uptake with advancing age in euthyroid patients revealed by these tests also runs parallel to the decrease in the basal metabolic rate (Robertson and Reid 1952) (fig. 2). An age-correction factor, such as is used for the basal metabolic rate, would therefore probably increase the sensitivity of the ^{131}I-excretion test. Our data suggest that in patients over 50, results in the " upper normal " range (T-index 9–13) may indicate hyperthyroidism.

Summary

^{131}I-excretion tests in a series of euthyroid patients were analysed. The results showed that the uptake of ^{131}I by the thyroid gland decreases with advancing age.

We gratefully acknowledge advice and assistance from Prof. Russell Fraser, and assistance in the statistical analysis from Mr. N. W. Please.

REFERENCES

Fraser, R., Hobson, Q. J. G., Arnott, D. G., Emery, E. W. (1953) *Quart. J. Med.* **22**, 99.
Perlmutter, M., Riggs, D. S. (1949) *J. clin. Endocrin.* **16**, 724.
Quimby, E. H., Werner, S. C., Schmidt, C. (1950) *Proc. Soc. exp. Biol., N.Y.* **75**, 537.
Robertson, J. D., Reid, D. D. (1952) *Lancet*, i, 940.

THE EFFECT OF INSULIN-BINDING ANTIBODIES ON INSULIN SENSITIVITY

N. KALANT, M.D. Toronto
C. GOMBERG, M.D. McGill
R. SCHUCHER, Ph.D. McGill

From the Department of Investigative Medicine, McGill University, and Research Laboratory, Jewish General Hospital, Montreal

BY the use of ^{131}I-labelled insulin, two abnormalities of insulin metabolism have been demonstrated in the sera of patients previously treated with insulin: (*a*) binding to serum-globulins (Berson et al. 1956), and (*b*) delayed disappearance from the circulation (Berson et al. 1956, Welsh et al. 1956). It has been suggested that repeated administration of insulin results in the formation of specific antibodies which migrate electrophoretically as globulins; injected insulin then becomes attached to the circulating antibody and is retained in the plasma instead of undergoing its normal course of degradation (presumably by tissue insulinase (Berson et al. 1956). Furthermore, since insulin must be in contact with cells to exert its biological action, it has been postulated that binding to antibody would prevent such contact and result in apparent insulin unresponsiveness (Welsh et al. 1956).

Various studies have clearly shown that patients with gross insulin resistance do have serum-globulin components which are probably antibodies, and which have an insulin-neutralising effect when injected with insulin into mice (De Fillipis and Iannocone 1952, Sehon et al. 1955, Colwell and Weiger 1956). But it is still uncertain whether the " ordinary " diabetic patient acquires a significant degree of resistance to insulin as the result of antibodies developing.

We have attempted to test the hypothesis concerning the effects of insulin antibodies and to determine the clinical significance of such antibodies.

Methods

The patients studied had maturity-onset diabetes (recognised after age 35), but no other recognisable metabolic disturbance. Fourteen had been treated with insulin for 6 months or longer, while eleven had not received insulin therapeutically.

Insulin responsiveness in the patients was determined by a procedure based on measurement of blood-glucose half-life (Heller, Kalant, and Hoffman). A glucose load was administered intravenously over 5 minutes, and 20 minutes was allowed for its equilibration in body fluids. During this interval a glucose infusion was given at a rate sufficient to maintain a raised blood-sugar concentration. Over the next 30 minutes samples of capillary blood were obtained every 5 minutes, and from these the rate of fall of blood-sugar and its half-life (t_1G) were calculated. Insulin [1] (0·1 u. per kg.) was then injected intravenously and sampling was continued for the next 30 minutes to permit calculation of blood-sugar half-life after insulin (t_1I).

In rabbits insulin responsiveness was assessed after the intravenous injection of crystalline insulin, 0·2 u. per kg., by measuring the blood-glucose concentration every 10 minutes for 90 minutes and determining, in arbitrary units, the area between the time-curve of glucose concentration and the baseline drawn at the level of the initial concentration. The dose of insulin was found by preliminary experiment not to produce a maximum hypoglycæmic effect in normal rabbits.

Paper electrophoresis of serum containing labelled insulin was performed using 50 μl. of serum applied in a line 3 inches toward the cathode from the middle of the strip, and allowed to move to the middle by hydrodynamic flow (Berson et al. 1956) before electrophoretic separation. The strips were dried and stained, and divided into eight sections: albumin, α_1, α_2, β, and γ globulins, a band extending 1 cm. on either side of the line of application (origin), the band between γ-globulin and origin, and a blank taken from the area on the anodal side of the albumin. Eight strips were run simultaneously for each sample of serum and the appropriate segments pooled for assay of radioactivity in a scintillation well counter.

Boundary electrophoresis was carried out in a Perkin-Elmer apparatus, model 38A, with barbitone buffer, pH 8·6, ionic strength 0·1. Aliquots of the serum were removed after resolution, by means of a needle-tipped pipette; by observation of the Schlieren pattern on the ground-glass screen it was possible to remove, from the descending limb, aliquots containing γ, $\gamma+\beta$, and $\gamma+\beta+\alpha_2$ globulin, and from the ascending limb those of albumin$+\alpha_1$ globulin, and of albumin$+\alpha_1+\alpha_2$ globulin. Each aliquot was measured for total protein, by buiret reaction or nitrogen determination, and for radioactivity. A concentration diagram of serum components was drawn from the Schlieren pattern and the relative composition of each aliquot removed from the electrophoresis cell was calculated (fig. 1).

1. Insulin labelled with ^{131}I was obtained commercially; it had a specific activity varying from 3 to 6 mc. per mg.

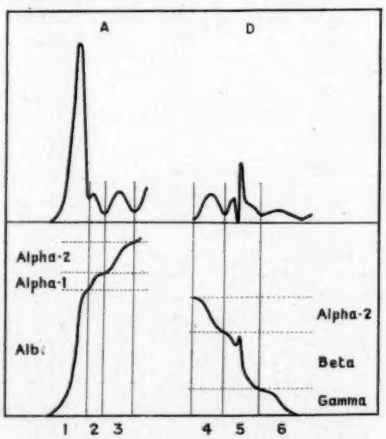


Fig. 1—Method of calculating specific activities of serum-proteins after separation by moving-boundary electrophoresis.

Above: Schlieren pattern. Below: Concentration diagram of serum components calculated from the Schlieren pattern. Specific activities of albumin and γ-globulin were calculated directly; their contribution of radioactivity to segments 2 and 5 were calculated, and specific activities of α_1 and β then obtained by difference. A: ascending limb. D: descending limb.

By reference to the total protein measurements it was then possible to calculate the actual composition of each aliquot.

The specific activities were measured directly for the first aliquot removed from each limb (γ-globulin from the descending and albumin-α_1 from the ascending). From the composition of the second aliquots ($\gamma+\beta$ from the descending, albumin$+\alpha_1+\alpha_2$ from the ascending) the contribution of γ and albumin-α_1 to the radioactivity of these fractions was calculated, and by difference the specific activity of β and α_2 were obtained. In some cases albumin was obtained separately from α_1-globulin; the specific activity of the latter was then calculated from the second ascending aliquot, and that of α_2 was taken as the mean value obtained from the third aliquots of each limb.

To study the rate of removal of insulin from plasma, a known amount of insulin-^{131}I was injected intravenously; the serum radioactivity precipitable by 10% trichloroacetic acid was measured 15 minutes later and expressed as percentage of injected dose present in the circulating plasma volume (as calculated from surface area and hematocrit) (Welsh et al. 1956). In the experiments on patients this procedure was used simultaneously with measurement of insulin responsiveness, the total dose of injected insulin (labelled+carrier) being that necessary for the latter purpose. In the rabbit experiments the two parameters were measured on different days. The choice of the 15-minute interval minimised the relative importance of radiation-damaged insulin, which apparently has a longer half-life in serum than does native insulin (Berson et al. 1956).

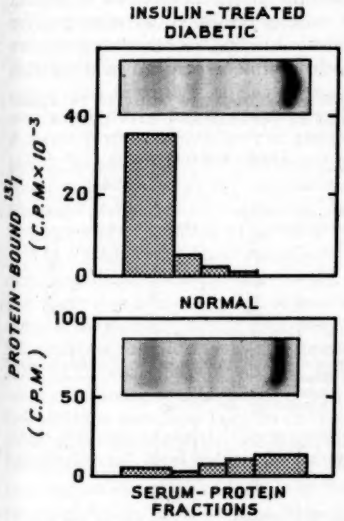


Fig. 2—Distribution of insulin-^{131}I among serum-proteins after separation by paper electrophoresis.

Rabbits were actively immunised against beef insulin[2] by the method of Arquilla and Stavitsky (1956). Passive immunisation was performed with plasma-proteins obtained from diabetic patients who demonstrated the phenomena of globulin binding and delayed disappearance of ^{131}I-insulin.

The plasma was treated with one-third volume of saturated ammonium sulphate; the precipitate was taken up in physiological saline solution and reprecipitated with ammonium sulphate. The precipitate was then redissolved in saline, dialysed against running tap water, and lyophilised for storage. At the time of use it was dissolved in physiological saline, cleared by centrifugation and infused into the femoral vein. The amount of protein in the infusions varied from 0·5 to 1·0 g. in 85–100 ml.

Insulin-neutralising activity of serum was assessed in groups of five mice previously fasted for 6 hours.

The glucose concentration of tail blood was measured before and 45 minutes after the intraperitoneal injection of insulin (2 or 6 milliunits in 0·01 ml.) mixed with 0·2 ml. of serum; the fall in glucose concentration was compared with that produced by the same amounts of insulin injected with 0·2 ml. saline. Blood-sugar was measured by Somogyi's (1952) modification of the Nelson method.

Results

Insulin Responsiveness in Diabetic Patients

In agreement with the results of Berson et al. (1956) it was found that the insulin-treated diabetic patients retained labelled insulin in their circulation longer than the untreated diabetic patients, and on paper electrophoresis most of it was found to be associated with γ-globulin. On electrophoresis of serum from untreated patients most of the radioactivity remined at the origin, and the remainder showed no preferential association with a particular protein component (fig. 2).

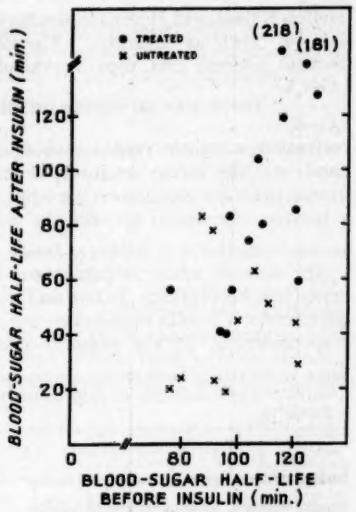


Fig. 3—Relation between half-life of blood-sugar before insulin and that after insulin (0·1 u. per kg.) in treated and untreated diabetic patients.

It has been previously shown for diabetics that, as the half-life of blood-glucose without insulin ($t_{\frac{1}{2}}G$) increases, there is a concomitant increase in the half-life after an injection of insulin ($t_{\frac{1}{2}}I$) (Heller, Kalant, and Hoffman). Consequently, to facilitate comparison of the insulin response of two groups, subjects having the same range of values of $t_{\frac{1}{2}}G$ were chosen. When they were thus selected, the untreated diabetic patients were found to have lower values for $t_{\frac{1}{2}}I$ (44±7 minutes) than the treated diabetic patients (94±14 minutes), indicating a greater fall in $t_{\frac{1}{2}}$ in response to insulin ($P<0.01$) in untreated diabetics (fig. 3 and table I).

The response to insulin may be defined as $(t_{\frac{1}{2}}G-t_{\frac{1}{2}}I)$; since in non-diabetic subjects $t_{\frac{1}{2}}I=20\pm6$ minutes

TABLE I—INSULIN RESPONSE, SERUM RETENTION, AND GLOBULIN-BINDING OF INSULIN IN TREATED AND UNTREATED DIABETIC PATIENTS

Patient	$t_{\frac{1}{2}}G$	$t_{\frac{1}{2}}I$	$\frac{t_{\frac{1}{2}}G-t_{\frac{1}{2}}I}{t_{\frac{1}{2}}G-20}$	Insulin in plasma at 15 min. (% of dose)	Insulin bound to globulin (% of plasma-insulin at 15 min.)
A–1	100	45	·69	11	5
A–2	111	51	·66	17	3
A–3	75	26	·89	16	5
A–4	76	20	1·00	17	0
A–5	92	23	·96	20	7
A–6	61	20	1·00	15	2
A–7	96	19	1·01	14	6
A–8	106	63	·50	14	3
A–9	122	29	·91	13	7
A–10	80	24	·93		
A–11	87	83	·06		
A–12	121	44	·76		
A–13	91	78	·18		
B–1	161	116	·32	35	54
B–2	121	85	·36	13	2
B–3	209	90	·63	25	33
B–4	274	168	·42	18	14
B–5	126	130	−·04	23	43
B–6	181	130	·32	63	37
B–7	98	56	·54	72	48
B–8	116	119	·03	81	62
B–9	97	83	·18	72	66
B–10	107	104	−·03		
B–11	76	56	·36		
B–12	128	127	·01		
B–13	94	41	·72		
B–14	96	40	·74		
B–15	115	218	−1·08		
B–16	124	181	−·55		
B–17	109	80	·33		
B–18	104	74	·36		
B–19	122	59	·62		

A=not treated with insulin.
B=treated with insulin.

2. Zinc insulin crystals were kindly supplied by Dr. W. R. Kirtley of Eli Lilly and Co., Indianapolis, Ind., and by Dr. R. G. Romans, Connaught Laboratories, University of Toronto.

(Heller, Kalant, and Hoffman), the normal insulin response may be taken as (t_4G–20). The relative response in diabetic patients can then be calculated as the ratio: $\frac{t_4G-t_4I}{t_4G-20}$. There was no significant degree of correlation between the insulin response so calculated, on the one hand, and the serum retention of insulin or binding of insulin to serum-globulin on the other (table II). There was a positive correlation between the latter two parameters.

Active Immunisation of Rabbits to Insulin

Six normal adult rabbits were immunised against crystalline beef insulin. Before and after this process, four parameters of insulin metabolism were studied: (1) insulin responsiveness, (2) the globulin-binding of insulin-^{131}I,

TABLE II—PARTIAL CORRELATIONS AMONG INSULIN RESPONSE, SERUM RETENTION AND GLOBULIN-BINDING OF INSULIN IN TREATED DIABETIC PATIENTS

—	r	P
Insulin response: globulin-binding of insulin ..	−0·3762	> 0·10
Insulin response: serum retention of insulin ..	+0·1130	> 0·10
Globulin-binding: serum retention of insulin ..	+0·7493	< 0·05

(3) the rate of disappearance from the circulation of injected insulin-^{131}I, and (4) the presence of circulating insulin-neutralising activity. In addition, the sera of the immunised rabbits was tested [3] for insulin antibodies by the method of Arquilla and Stavitsky (1956). The results (table III) indicate that immunisation led to the development of hæmagglutinating antibodies to insulin, a decrease in the rate of disappearance of insulin from the circulation, and globulin-binding. There was a direct relation between the amount of insulin remaining in the plasma 15 minutes after administration and the proportion of this which was "bound" to serum-globulin (fig. 4). After immunisation

3. Dr. E. R. Arquilla and Dr. A. B. Stavitsky kindly carried out these tests.

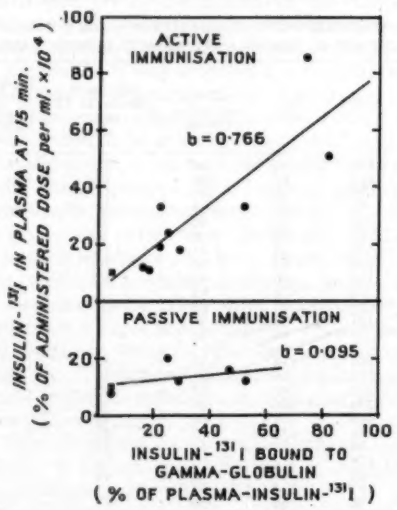


Fig. 4—Relation between insulin-^{131}I in plasma 15 minutes after administration and the amount of that insulin associated with γ-globulin on paper electrophoresis.

Upper: results of 9 tests in six rabbits actively immunised by repeated injection of insulin. Lower: Results in five rabbits passively immunised by infusion of serum-proteins from insulin-treated diabetic patients. Symbol (•) in lower left corner represents mean normal values.

TABLE III—EFFECTS OF ACTIVE IMMUNISATION ON INSULIN METABOLISM

Animal no.	Insulin response (area, arbitrary units)		Insulin retention (% of dose remaining in plasma at 15 min.)		Globulin-binding (% of plasma insulin-bound to γ-globulin)		Hæmagglutinating antibody (titre)
	Before	After	Before	After	Before	After	After immunisation*
1	705	1145	..	19	2·9	22·1	512, 256
2	112	603	8	86	5·5	73·5	512, 512
3	1288	2299	12	33	3·9	22·4	512, 256
4	530	1070	11	18	5·4	29·1	512, 256
5	735	227	8	51	5·4	82·1	256, 512
6	885	915	12	33	4·7	52·0	512, 512

* Determinations were done on aliquots of serum taken 4 days apart.

five of the six animals showed an increase in insulin responsiveness, but the mean change was not significant at the 5% level. None seemed to have developed a measurable titre of insulin-neutralising activity (table IV).

Passive Immunisation of Rabbits to Insulin

Globulin-binding and the disappearance rate of insulin were studied in five rabbits 36–40 hours after passive immunisation with insulin-binding serum obtained from diabetic patients. Such treatment resulted in a variable

TABLE IV—ASSAY FOR INSULIN-NEUTRALISING ACTIVITY IN RABBIT SERUM BEFORE AND AFTER IMMUNISATION WITH INSULIN

Animal	Insulin dose (milliunits)			
	2		6	
	Before	After	Before	After
1	36	38	50	53
2	16	23	25	46
3	25	12	53	29
4	11	27	25	61
5	22	42	41	76
6	..	24	..	39

Values represent the mean fall in blood-sugar (mg. per 100 ml.) in five mice 45 minutes after injection of serum-insulin mixture. The fall in blood sugar produced by insulin alone was:
2 milliunits, 13±10 mg.
6 milliunits, 30±15 mg.

increase in globulin-binding of ^{131}I-insulin but did significantly slow the removal of insulin from the circulation (fig. 3).

Location of Insulin-binding Globulin

Characteristic examples of the results obtained on fractionation of serum-insulin-^{131}I mixtures by moving-boundary electrophoresis are shown in table V. When serum from a non-diabetic subject was used, the insulin moved principally with the albumin and α_1-globulin. With serum from an insulin-treated diabetic patient, the insulin was associated principally with the β-globulin, although on paper electrophoresis it apparently moved with γ-globulins. Addition of excess insulin to diabetic serum resulted in movement of radioactivity with all protein fractions; when the serum-insulin mixture was passed through a powdered cellulose column (15 × 0·8 cm.) most of the radioactivity remained on the column, and that which passed through the column with the serum showed the expected association with β-globulin on subsequent free electrophoresis. These results confirm by boundary

TABLE V—DISTRIBUTION OF INSULIN-^{131}I IN SERUM AFTER ELECTROPHORESIS

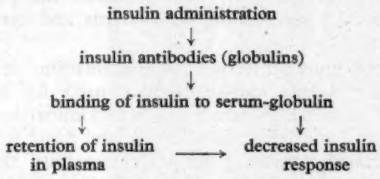
—	Albumin	α_1	α_2	β	γ
Normal serum	58	17	5	16	3
Diabetic serum	3	4	3	83	7
Diabetic serum + excess insulin ..	17	27	34	20	2
Diabetic serum + excess insulin passed through cellulose column	17		8	65	9

Values represent percentage of total serum activity.

electrophoresis the results obtained with paper electrophoresis (Berson et al. 1956) and alcohol fractionation (Berson and Yalow 1957).

Discussion

The hypothesis under examination may be expressed diagrammatically thus:



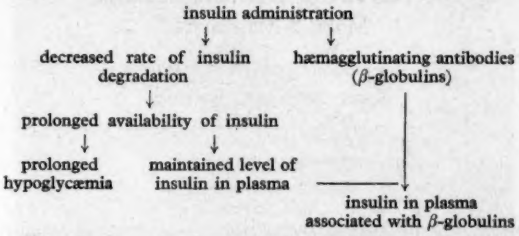
Diabetic patients previously treated with insulin had less response to insulin than diabetics who had comparable impairment of carbohydrate tolerance (t_1G the same in both groups) but had not been treated with insulin. This finding is compatible with the above hypothesis. However, contrary to what might have been expected, there was no apparent correlation between insulin response and degree of binding of insulin to serum-globulin. Furthermore, the untreated subjects were for the most part newly discovered diabetics, and possibly they would have shown a further impairment of insulin response with time alone. In addition, since diabetes is not a disease entity of single ætiology, there are undoubtedly several unknown and uncontrolled factors affecting insulin responsiveness in groups of patients such as these.

The likelihood of such variation was less in the rabbit experiments, in which normal animals were used. Here it is evident that administration of insulin led to the development of hæmagglutinating antibodies, to globulin-binding of insulin, and to delayed disappearance of insulin from the circulation. Except for one animal, however, there was no evidence of diminution of response to insulin, and indeed there may have been an increased response. Moreover, after immunisation there was no evidence of circulating insulin-neutralising activity. It therefore appears that neither retention of insulin in the plasma, binding to serum-globulin, nor the presence of hæmagglutinating antibodies to insulin inhibits the action of insulin.

The low incidence of insulin resistance in these animals is comparable to that obtained by Lowell and Franklin (1949) with similar methods in a larger group of animals. Moloney and Coval (1955) were also unable to produce insulin-neutralising antibodies in the rabbit.

The infusion into rabbits of serum-proteins from treated diabetic patients resulted in "passive transfer" of globulin-binding of insulin, but not of retention of insulin in the circulation. Hence we may conclude that binding of insulin by globulin is not the cause of insulin retention.

The results described are not compatible with the hypothesis as stated above, but are compatible with an alternative hypothesis. This is that long-continued administration of insulin results in two abnormalities: (*a*) a primary decrease in the rate of insulin degradation, leading to passive retention of insulin in the circulation and to a prolonged insulin effect, and (*b*) the appearance of circulating antibodies which form with insulin a loose complex which does not inhibit either degradation or the association of insulin with tissues, and consequently does not inhibit the response to insulin or affect the rate of its removal from the circulation. The latter phenomenon does not conform to the generally accepted idea that antibody increases the rate of removal of antigen from the circulation, and suggests that the insulin-binding globulin may not in fact function as an antibody in the usual sense. These relationships may be presented schematically:


insulin administration
decreased rate of insulin degradation
hæmagglutinating antibodies (β-globulins)
prolonged availability of insulin
prolonged hypoglycæmia
maintained level of insulin in plasma
insulin in plasma associated with β-globulins

The decrease in the rate of degradation may be due to a humoral factor, since plasma from patients showing insulin retention can apparently inhibit insulin degradation in vitro (Welsh et al. 1956).

Such a hypothesis is not incompatible with certain diabetics having insulin resistance, of varying degree, related to the formation of antibodies; but such antibodies appear to differ from those which are only the result of repeated administration of insulin.

The electrophoretic analyses confirm the finding of Berson and Yalow (1957) that the "insulin-binding protein" is a β-globulin rather than a γ-globulin. When the binding capacity of this protein was reached, excess insulin travelled with other proteins in a non-specific manner; exposure to cellulose removed the "excess" insulin, so that the remainder had the expected distribution pattern. It must be emphasised that the actual specific activity values obtained for γ-globulin and albumin may be considered accurate; but the remainder, being obtained by difference, are only approximations.

Conclusions

1. Diabetic patients previously treated with insulin had less insulin response than diabetic patients who had not been previously treated. The insulin response was apparently not related to the degree of globulin-binding of insulin or to the degree of insulin retention in the circulation.

2. Repeated injection of insulin into normal rabbits led to the development of hæmagglutinating antibodies to insulin; the removal of insulin from the circulation was altered, and binding of insulin to serum-globulin was demonstrable. There was no evidence of a decrease in the hypoglycæmic response to insulin or of the presence of anti-insulin activity in the serum.

3. Infusion, into normal rabbits, of serum obtained from insulin-treated diabetics led to the globulin-binding of insulin but did not alter the rate of insulin removal.

4. It is concluded that insulin-binding antibodies and hæmagglutinating antibodies are not responsible for decreased responsiveness to insulin or for its slower removal from the circulation.

5. Moving boundary electrophoresis indicates that the insulin-binding antibodies are β-globulins.

REFERENCES

Arquilla, E. R., Stavitsky, A. B. (1956) *J. clin. Invest.* **35**, 458.
Berson, S. A., Yalow, R. S. (1957) *ibid.* **36**, 642.
— — Bauman, A., Rothschild, M. A., Newerly, K. (1956) *ibid.* **35**, 170.
Colwell, A. R., Weiger, R. W. (1956) *J. lab. clin. Med.* **47**, 844.
De Fillipis, V., Iannocone, A. (1952) *Lancet*, i, 1192.
Heller, N., Kalant, N., Hoffman, M. M. *J. lab. clin. Med.* (in the press).
Lowell, F. C., Franklin, W. (1949) *J. clin. Invest.* **28**, 199.
Moloney, P. J., Coval, M. (1955) *Biochem. J.* **59**, 179.
Sehon, A. H., Kaye, M., McGarry, E., Rose, B. (1955) *J. lab. clin. Med.* **45**, 765.
Somogyi, M. (1952) *J. biol. Chem.* **195**, 19.
Welsh, G. W., Henley, E. D., Williams, R. H., Cox, R. W. (1956) *Amer. J. Med.* **21**, 337.

MONILIAL PERITONITIS AS A COMPLICATION OF PREOPERATIVE INTESTINAL STERILISATION

MOGENS ANDREASSEN
M.D. Copenhagen
OF RIGSHOSPITALET, COPENHAGEN

KNUD RIEWERTS ERIKSEN
M.D. Copenhagen
OF THE INSTITUTE FOR GENERAL PATHOLOGY, UNIVERSITY OF COPENHAGEN

AKSEL STENDERUP
M.D. Aarhus
OF THE INSTITUTE FOR GENERAL PATHOLOGY, UNIVERSITY OF AARHUS

MONILIAL peritonitis seems to be very rare. We have only been able to find one published case (Reynell et al. 1953). The patient was a man, aged 49, who was treated with corticotrophin and aureomycin for suspected periarteritis nodosa and had a duodenal ulcer. After three days' treatment peritonitis developed, and the patient died four days later. Necropsy revealed a perforated duodenal ulcer and peritonitis; *Candida albicans* was cultured from the peritoneal cavity. It was assumed that the chemotherapy had changed the intestinal flora in favour of *C. albicans*, which entered the peritoneal cavity through the perforated ulcer and caused the infection.

We have observed a similar case, which is described below.

Case-report

A girl, aged 4 years, had had sluggish bowel movements since birth. For six months before admission her constipation increased in severity, becoming associated with abdominal distension, attacks of pain, and vomiting. Radiography having revealed megacolon, an operation was advised. From the day before operation phthalylsulphathiazole 3 g. six times daily for two days and duostreptomycin 1 ml. thrice daily for seven days were given orally together with procaine penicillin 200,000 units daily.

Operation revealed segmental dilatation, mainly of the transverse colon, the lower portion of the descending colon, the sigmoid, and the rectum being normal. The colon was resected from 8 cm. above the iliocæcal valve to the lower portion of the descending colon, with end-to-end anastomosis.

Postoperative course.—The immediate postoperative course was uneventful; but on the eighth day pyrexia developed, for which reason the dosage of penicillin was increased to 1,000,000 units twice daily. On the eleventh postoperative day increasing pneumoperitoneum, with distended abdomen but without peritoneal reactions, was noted. It was supposed to be due to a small leakage at the site of the anastomosis; but, owing to the surprisingly good general condition of the patient and the absence of signs of peritonitis, further developments were awaited. During the next few days the patient began to whimper; the abdominal distension increased, and incipient paralytic ileus developed, but signs of peritonitis were still absent (temperature 38·2°C).

Reoperation on the sixteenth postoperative day revealed a peculiar diffuse inflammation with dense adhesions of the intestines. The picture did not resemble that of purulent peritonitis; pus was absent, but the intestines were covered by dry fibrinous flakes. The anastomosis was found to be leaking slightly; so the anastomosis was transformed into a colostomy. Culture of material from the peritoneal cavity yielded a heavy growth of *C. albicans* but no bacteria.

Postoperatively gastric paralysis developed, but intestinal function was resumed on the fourth postoperative day. Pus discharged from the colostomy for some time; cultures of it produced *C. albicans*, proteus, and enterococci. Chemotherapy with various drugs led to gradual improvement, and the patient was discharged cured four months after the first operation.

Discussion

It can scarcely be doubted that the chemotherapy given immediately before and after the first operation had changed the intestinal flora, with the result that it mainly consisted of *C. albicans*, which entered the peritoneal cavity through the leaking anastomosis and caused the peritonitis.

It is well known that various combinations of chemotherapeutic agents and antibiotics used for so-called intestinal sterilisation before major abdominal operations only remove the intestinal bacteria, the fungi normal to the intestines continuing to proliferate until they ultimately constitute the greater part of the intestinal flora. Although fungi are usually considered to be of low virulence, they may, as in the present case, give rise to severe infection. It must be assumed that the peritoneum was not contaminated during the operation, but that the intestinal leakage persisted for some time, during which large amounts of *C. albicans* entered the peritoneal cavity.

The chemotherapy used has no effect on the fungi. It may therefore seem strange that the patient, who had severe peritonitis, recovered. However, the human body usually has a strong resistance to *C. albicans*, and the peritonitis presumably developed only because fungi had constantly entered the peritoneal cavity before the colostomy was established.

Cases of this type are undoubtedly rare; but the case reported here shows that preoperative intestinal sterilisation is not without hazards.

Summary

A case of monilial peritonitis in a girl, aged 4 years, whose colon had been resected for megacolon, is reported. It is assumed that preoperative chemotherapy to sterilise the intestine changed the intestinal flora, with the result that it mainly consisted of *C. albicans*, which penetrated into the peritoneal cavity through a leaking intestine.

REFERENCE

Reynell, P. C., Martin, E. A., Beard, A. W. (1953) *Brit. med. J.* i, 919.

EFFECT OF A LAMINARIN SULPHATE (LM 46) ON BONE GROWTH

S. S. ADAMS
Ph.D. Leeds

HAZEL M. THORPE
B.Sc. Lond.

OF THE BIOLOGY DIVISION, RESEARCH DEPARTMENT, BOOTS PURE DRUG CO. LTD., NOTTINGHAM

L. E. GLYNN
M.D. Lond., M.R.C.P.
DIRECTOR OF PATHOLOGY, RHEUMATIC RESEARCH UNIT (M.R.C.), CANADIAN RED CROSS MEMORIAL HOSPITAL, TAPLOW, BUCKS

LAMINARIN is a polysaccharide consisting of approximately 20–30 glucose units joined by β–1 : 3 linkages, and occasionally a β–1 : 6 linkage (Connell et al. 1950, Percival and Ross 1951, Friedlaender et al. 1954). It is obtained from certain brown seaweeds and occurs in two forms—" soluble laminarin " from *Laminaria digitata*, and " insoluble laminarin " from *L. cloustoni*. The latter can be sulphated to produce soluble compounds with varying numbers of sulphate groups per glucose unit. Several of these products have been examined previously for anticoagulant activity and toxicity, both of which increase with sulphation (Adams and Thorpe 1957).

We have studied in more detail other laminarin sulphates prepared from laminarin derived from *L. cloustoni*, one of which—LM 46—was more toxic and more highly sulphated than the others. Initial experiments revealed that this compound had an anticoagulant activity equivalent to 33 heparin units per mg. when tested by the sulphated whole blood method (Adams and Smith 1950). The acute intravenous L.D.50 to mice was approximately 1500 mg. per kg., but the "anaphylactoid" reaction (Walton and Ricketts 1954) was produced in guineapigs by intravenous doses of 100 mg. per kg. body-weight. These results are similar to those reported for laminarin sulphate K (Adams and Thorpe 1957). However, on protracted dosing to rabbits, guineapigs, and rats, LM 46 produced effects which were quite different from those reported for other laminarin sulphates, and which we believe have not been recorded previously for sulphated polysaccharides. We give here a preliminary report of these findings, particularly of the skeletal changes.

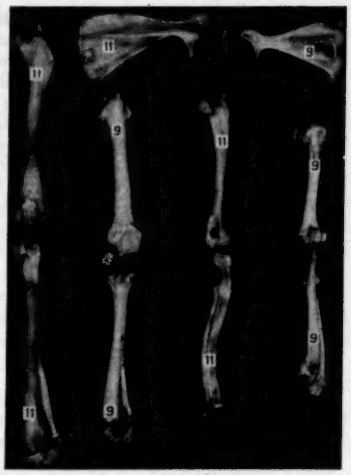


Fig. 1—Bones (a) from rabbit (9) treated with LM 46 30 mg. per kg. intravenously daily for 24 days; (b) from control rabbit (11) which received heparin 10 mg. per kg. intravenously daily for 23 days.

Note small size of bones from rabbit treated with LM 46 and considerable deformity of bone ends, especially at knee and shoulder.

Methods

LM 46 was administered subcutaneously or intravenously to rabbits, guineapigs, and rats on 5 days of each week for 2–9 weeks. Rabbits received 15, 30, and 60 mg. per kg. body-weight, rats 15 and 30 mg. per kg., and guineapigs 15 mg. per kg. daily. The ages of the animals at the start of the experiments were rabbits 6–8 weeks, rats 3–4 weeks, and guineapigs 6–8 weeks. Control animals, littermates in the case of the rabbits, received a dose of heparin equivalent in anticoagulant activity to the laminarin sulphate.

When the animals became moribund they and the heparin controls were killed with intravenous barbiturate, and soft tissues and long bones were taken for histological examination. The remainder of the skeleton was retained for preparation of dry bone specimens.

Fig. 2—Epiphyseal plate at lower end of fenur of rat treated for 49 days with laminarin sulphate LM 46 at 15 mg. per kg. subcutaneously daily. (Hæmatoxylin and eosin ×75.)

There has been complete arrest of maturation of cartilage with consequent failure of endochondral bone formation in metaphysis.

Results

In all animals there was a pronounced loss of weight after prolonged dosing, and they seemed very frail both in appearance and when handled. The rabbits and guineapigs had a white discharge in the eyes.

The most interesting effects, however, were the skeletal abnormalities, which were most striking in the rabbits,

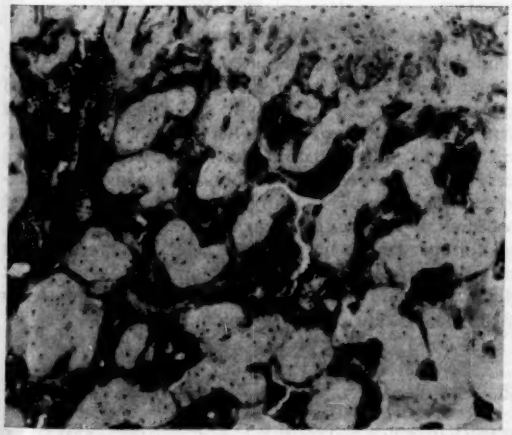


Fig. 3—Epiphyseal plate at lower end of femur of control rat treated with heparin at 10 mg. per kg. subcutaneously daily for 49 days. (Hæmatoxylin and eosin ×75.)

Endochondral ossification is proceeding normally, resulting in rich network of newly formed bone trabeculæ in metaphysis.

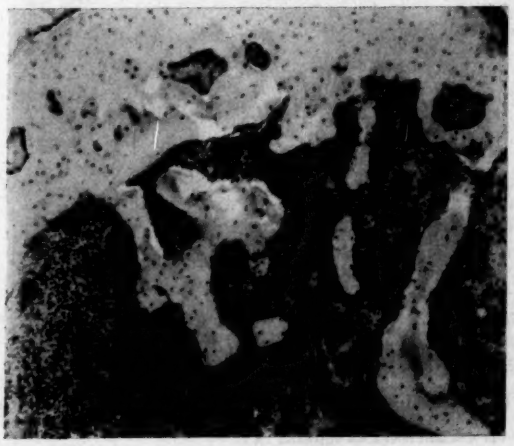


Fig. 4—Lower epiphysis of same femur as in fig. 2. Bone trabeculae normally present have been almost completely removed. (Hæmatoxylin and eosin ×75.)

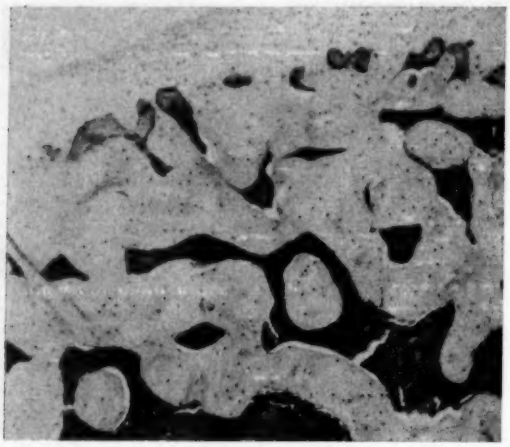


Fig. 5—Lower epiphysis of the same femur as in fig. 3. Rich network of bone trabeculae is in striking contrast to that in fig. 4. (Hæmatoxylin and eosin ×75.)

sometimes after only a few days of dosing. Initially, the carpal joints became knobbly, and later the condition worsened until these joints were grossly abnormal and caused pronounced splaying of the feet either inwards or outwards. Later there was weakness in the pelvic region which sometimes developed into complete paralysis. In some animals the femur fractured.

In rats the 15 mg. per kg. dose produced its effects more slowly than in the rabbit, and the forelimb distortion was less obvious; but there was definite weakness in the pelvic region, and distinct kyphosis developed. In guineapigs the effects were similar to those in the rabbit, but they appeared more gradually.

Both macroscopically (fig. 1), and histologically the changes were greatest at the growing ends of the long bones. In guineapigs and rats normal maturation of the cartilage cells in the epiphyseal plate was lacking, and there was deficient invasion of this zone by capillaries from the adjacent marrow. There was, in consequence, almost complete absence of new bone trabeculæ

Fig. 6—Shoulder-joint of rabbit treated for 24 days with laminarin sulphate LM 46 at 30 mg. per kg. intravenously daily. (Hæmatoxylin and eosin ×3 approx.)

Head of humerus has collapsed owing to absorption of bone trabeculæ in head, and defective endochrondal bone formation in metaphysis. Epiphyseal plate is itself disrupted into several fragments.

in the metaphysis (figs. 2 and 3). There was simultaneous loss of bone trabeculæ in the epiphysis (figs. 4 and 5), which, in extreme cases, was reduced to a shell of cortical bone enclosing the vascular marrow. The epiphysis then collapsed (fig. 6), and this resulted in pronounced deformity of the articular surface with hæmorrhage and necrosis of the epiphyseal marrow. Similar but less severe hæmorrhages and necrosis were sometimes seen in the metaphysis. In rabbits the maturation of the cartilage cell columns appeared normal, but very little bone was deposited on the cartilaginous trabeculæ despite striking hyperplasia of osteoblasts in the metaphysis. Necrosis commonly overtook these defective bone trabeculæ.

In addition to the bone lesions all the animals showed accumulation of metachromatic material in the reticuloendothelial system and in the proximal convoluted tubules of the kidneys.

Discussion

The bone lesions that develop after repeated injections of this particular laminarin sulphate appear to depend primarily on disturbance of the endochondral bone formation that normally takes place on the diaphyseal side of the epiphyseal cartilage. In rats and guineapigs the normal sequence of maturation of the cartilage cells is impaired, and this is associated with virtually complete absence of the vascular invasion that normally precedes the actual deposition of bone on the newly formed tongues of calcified cartilage. In rabbits it is apparently this deposition of bone which is impaired. It is not at present possible to say how these disturbances are brought about by the laminarin sulphate; but its structural similarity to chondroitin sulphate suggests that it might be acting by interfering with the normal metabolism of chondroitin sulphate, especially at sites where the turnover-rate of the normal polysaccharide is high. There is, moreover, some evidence that the effect of this laminarin sulphate may be shared by other sulphated polysaccharides. Thus, L. L. Coleman (cited by Regelson and Holland 1958) found osteoporosis in rabbits receiving injections of either polyethylene sulphonate or heparin, and fractures in cholesterolfed rabbits receiving repeated injections of heparin have been reported by Gillman and Naidoo (1957). A study of the mechanism by which these sulphated polysaccharides produce bone lesions should provide valuable information about the normal processes of endochrondral bone formation.

Addendum

Since this paper was prepared H. C. Hint and A. W. Richter (*Brit. J. Pharmacol.* 1958, **13**, 109) have reported similar findings in the rabbit following the chronic administration of dextran sulphate. They do not, however, refer to forelimb deformities such as we have reported here, and which we have also found following the administration of clinical-size dextran sulphate. We have noted that forelimb deformities occur only in very young rabbits, and for that reason used animals aged 6–8 weeks. Hint and Richter used animals 5–6 months old—an age at which we would not expect the forelimb deformities to be obvious, except perhaps at necropsy.

REFERENCES

Adams, S. S., Smith, K. L. (1950) *J. Pharm. Pharmacol.* **2**, 836.
— Thorpe, H. M. (1957) *ibid.* **9**, 459.
Connell, J. J., Hirst, E. L., Percival, E. G. V. (1950) *J. chem. Soc.* p. 3494.
Friedlaender, M. H. G., Cook, W. H., Martin, W. G. (1954) *Biochim. biophys. Acta*, **14**, 136.
Gillman, T., Naidoo, S. S. (1957) *Nature, Lond.* **179**, 904.
Percival, E. G. V., Ross, A. G. (1951) *J. chem. Soc.* p. 720.
Regelson, W., Holland, J. F. (1958) *Nature, Lond.* **181**, 46.
Walton, K. W., Ricketts, C. R. (1954) *ibid.* **173**, 31.

Preliminary Communication

A SINGLE-PUMP BUBBLE OXYGENATOR

THE deliberate foaming of blood as a means of oxygenation was described by Schroeder [1] in 1882, but the principle was not applied to extracorporeal circulation until 1956. The description by De Wall et al.,[2] of a disposable bubble oxygenator coupled with the fixed-low-flow principle, developed in their cross-circulation work, has been followed by a series of modifications of the apparatus.[3–6]

We record here some further modifications which have evolved in the course of our experimental [7 8] and clinical experiences and which have been dictated by the need for simplicity and economy.

APPARATUS

In the original circuit [2] the venous blood was aspirated from the venæ cavæ directly to a 'Sigmamotor' pump. With such aspiration, adherence of the caval walls to the orifices of the catheters often interfered with venous return. We have got over this difficulty by using gravity drainage into a venous reservoir—which has incidentally simplified adjustment of the pumps during bypass. We have found it possible to eliminate the venous pump and to rely on gravity to return the venous blood to the reservoir and thence to the oxygenator column. The whole apparatus is lowered so that the top of the oxygenator column is below the level of the right atrium (fig. 1).

1. Schroeder, v. N. *Arch. exp. Path. Pharmak.* 1882, **15**, 364.
2. De Wall, R. A., Warden, H. E., Gott, V. L., Ziegler, N. R., Varco, R. K., Lillehei, C. W. *Surg. Clin. N. Amer.* 1956, **36**, 1025.
3. Gammelgard, R. A., Husfeldt, E., Therkelsen, F. *Acta chir. scand.* 1957, **112**, 439.
4. Gott, V. L., De Wall, R. A., Paneth, M., Nazhi Zuhdi, M., Weirich, W., Varco, R., Lillehei, C. W. *Thorax*, 1957, **12**, 1.
5. Cooley, D. A., Belmonte, B. A., Latson, J. R., Pierce, J. F. *J. thorac. Surg.* 1958, **35**, 131.
6. Giannelli, S., Jr., Molthan, N. F., Best, R. J., Dull, J. A., Kirby, C. K. *ibid.* 1957, **34**, 563.
7. Taylor, D. G. *Guy's Hosp. Rep.* 1958, **107**, 100.
8. Taylor, D. G. Cavanagh, J. B. Unpublished.

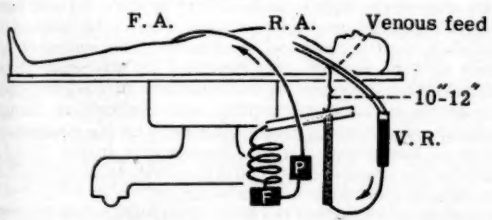


Fig. 1—Showing the relation between the pump oxygenator and the patient.

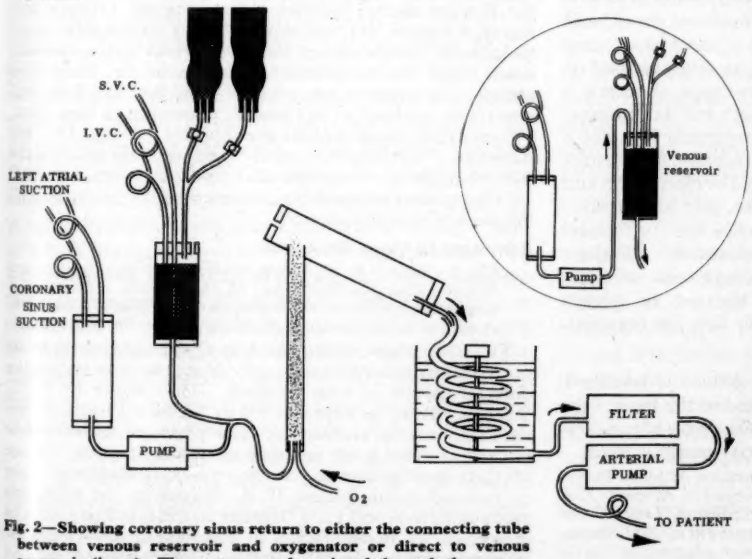


Fig. 2—Showing coronary sinus return to either the connecting tube between venous reservoir and oxygenator or direct to venous reservoir (inset). The system can be primed through the venous or coronary-sinus reservoirs. The lead from coronary-sinus reservoir to external suction is not shown.

CARDIOPULMONARY BYPASS SURVIVAL EXPERIMENTS USING GRAVITY DRAINAGE AND ONE PUMP

Dog	Weight (kg.)	Flow (ml. per min.)	Bypass (mins.)	Blood-pressure (mm. Hg)	Survival-time
1	11·5	1200	14	..	12 hours
2	13·0	1500	24	110	8 days (killed)
3	9·8	500	22	40–80	7 days (killed)
4	10·5	600	20	45–100	8 days (killed)
5	8·9	550	20	40–100	5 days (died)
6	9·0	600	20	40–90	12 hours
7	13·3	700	20	70	4 hours
8	9·9	530	20	40–90	6 days (killed)
9	9·0	450	20	60	7 days (killed)
10	9·7	500	20	..	6 days (killed)

Elimination of the venous pump removes a source of blood trauma.

Under experimental conditions in our laboratory, a single T6S sigmamotor pump set at an output of 1 litre per minute, with a priming volume of 1 litre of dog blood, will produce 50–70 mg. of free hæmoglobin per 100 g. of blood after 1 hour. With a priming volume of 2 litres, and a flow of 2 litres per minute for 1 hour, it will produce 200–250 mg.

To reduce the blood damage we have substituted for the sigmamotor pump a commercially available British-made 'Mono' pump, which utilises the archemedian screw principle. The use of this pump has a sound theoretical basis [9] and it has given excellent results in our hands (see table).

It gives a continuous flow of up to 6 litres per minute and can maintain a constant output against a head of pressure of 90 feet of water. A standard production model B15 has been used, but sterile assembly of the unit has introduced some difficulties. The manufacturers are now developing a unit which can be easily autoclaved and assembled. At present the pump is driven by a $^1/_4$ h.p. single-phase 240-volt A.C. motor of 960 r.p.m. through a Kopp 'Variator' to give a range of output from 700 to 5000 ml. per minute.

The coronary-sinus return is collected in an evacuated reservoir of conventional type maintained at a negative pressure of 3 cm. of mercury by a separate suction pump. From the bottom of this reservoir the blood is pumped by a hand-operated roller pump to the venous reservoir. The circuit is primed by sucking filtered blood into the coronary-sinus reservoir and pumping it into the venous reservoir (fig. 2).

The oxygenator column has an internal diameter of

9. Hall, J. E., James, P. A., Lucas, B. G. B., Waterson, D. J. *Thorax*, 1958, **13**, 1.

$1^1/_2$ in. and the tube connecting it to the venous reservoir has an internal diameter of $^1/_2$ in.

RESULTS

This simplified circuit has been used on ten dogs and there have been seven survivors. In the first experiment a filter was not used but in the remainder one has been incorporated in the base of the helix. The amount of debris found on the filter at the end of each bypass has varied considerably, for no apparent reason. In the sixth experiment there was insufficient blood to prime the circuit and the operating level in the helix was around 200 ml. There should be at least 1 minute's flow volume in the helix to reduce the possibility of micro-bubbles being drawn into the arterial line. The seventh dog died from a pulmonary embolus arising from the right atrial appendage. A clamp had been applied to the appendage and two purse-string sutures inserted 20 minutes before heparin was given.

The apparatus used in clinical cases has now been modified similarly. Two patients (a tetralogy of Fallot and a ventricular septal defect) have been operated on using the modified oxygenator circuit and a single sigmamotor pump. The patient in whom the ventricular septal defect was closed is alive and well. The patient with tetralogy of Fallot died 24 hours after attempted complete correction. Consciousness was regained and death is not attributed to the perfusion technique.

DISCUSSION

Doubts have been expressed about the safety of bubble oxygenation,[10 11] but in view of its successful clinical application we decided to retain this technique while simplifying the circuit.

The substitution of gravity drainage for pump suction immediately removed one of the main sources of anxiety during bypass. While the venous pump was always carefully balanced against the arterial, frequent variations in the venous return necessitated continual adjustment of the venous pump. With gravity drainage and elimination of the venous pump the circulation adjusts itself automatically and in a much shorter time.

The hæmolysis caused by the sigmamotor pump, and its limited output, prompted the trial of the Mono pump which has a low hæmolysis factor, is cheaper, and is readily obtainable in this country. Its range of output is adequate for all prospective bypass cases and its constant-flow delivery is a superior means of returning blood to a patient through a narrow cannula. A pulsatile flow results in peaks of high pressure in the tubing between pump and patient at the top of the input stroke, and at the same time the jet injected through the cannula into the femoral artery gives rise to considerable turbulance. All these factors must be harmful to the blood and seem unnecessary when one considers that at the site of oxygen exchange in the capillaries the pulsatile flow has been lost.

SUMMARY

A simplified circuit for a bubble oxygenator is described. Blood from the venæ cavæ is conducted to the base of the oxygenator by gravity, so that a venous pump is unnecessary. For the arterial return a ' Mono ' pump is used.

We would like to acknowledge the cooperation of Mono Pumps Ltd., who supplied a pump for protracted trial; of Allspeeds Ltd. (Oakenshaw Works, Clayton-Le-Moors, Accrington, Lancs.), who provided a Kopp variator; and of the department of medical illustration, Guy's Hospital. The two patients were operated on by Sir Russell Brock, whose continued support and encouragement have made this work possible.

M. H. CASS *
M.B. Sydney
D. N. ROSS
M.B., B.SC. Cape Town, F.R.C.S.
D. G. TAYLOR
M.B. Belf., F.R.C.S.
Thoracic Surgical Unit, Guy's Hospital, London, S.E.1

* During tenure of medical postgraduate training fellowship of the University of Sydney. Present address: Royal Children's Hospital, Melbourne, Australia.

10. Diesh, G., Flynn, P. J., Marable, S. A., Molder, D. G., Schmutzer K. J., Longmire, W. P., Jr., Maloney, J. V. *Surgery*, 1957, **42**, 67
11. Jordan, F., Jr., Tolstedt, G. E., Beretta, F. F. *ibid.* 1958, **43**, 266.

Reviews of Books

Doctor and Patient in Soviet Russia

MARK G. FIELD, PH.D., with a foreword by PAUL D. WHITE, M.D. Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1958. Pp. 266. 40*s*.

Dr. Field has spent only a month in Russia, but at the Russian Research Center at Harvard University he has made a long study of Soviet books and journals, has interviewed many doctors who have left Russia, and has analysed answers to a questionary addressed to 1650 former Soviet citizens. His book is described as a study not of Soviet medicine but in the sociology of the medical profession; but as such it is the most penetrating commentary on medical Russia that we have seen. Soviet medicine provides, he says, almost the extreme example of interference with the doctor's work. Since the revolution Russia has been a mobilised society in which (as in war-time here) priorities at all levels have been laid down by the leaders. Medicine had to be controlled in order that its practice should fit the aims of the regime, and, so long as the chief aim was intensive industrial production, doctors were under particular pressure in their certification of sickness. The resistance of doctors to State pressure was weakened by abolishing their professional organisations, by indoctrination of students, and by reducing the doctor's prestige and standard of living. Dr. Field notes a striking resemblance between the position of doctors in Russia and that of schoolteachers in the U.S.A. Admitting the advantages of central direction, he describes the harm done by red tape, and by the setting of " norms " in practice, and he also describes the gross differences in the kind of medical care given to different classes. Yet, after forty years' vicissitudes the tradition of personal service has survived in the Russian doctor; comparing him with his German colleague, a refugee said that, though he has no complex equipment, he is " much warmer and more serious and, in the end, much better for the patient ". Though, as Dr. Field fully realises, the evidence of refugees from the U.S.S.R. will scarcely be unbiased, of 617 émigrés questioned in New York, 50% preferred Soviet medical arrangements and only 18% the American. " In the Soviet Union ", said one, " the doctor is the slave of the State. . . . In America he is the slave of the dollar."

In many ways a formidable indictment of the Soviet system, this book is scrupulously fair.

Advances in Virus Research

Vol. 5. Editors: K. M. SMITH, virus research unit, Agricultural Research Council, Cambridge; M. A. LAUFFER, department of biophysics, University of Pittsburgh, Pennsylvania. New York: Academic Press. London: Academic Books. Pp. 376. 76*s*.

THE fifth volume is very much up to the standard set by its predecessors, and continues to provide authoritative reviews on different aspects of virus research. The chapter by G. S. Stent on Mating in Reproduction of Bacterial Viruses is outstanding, and the synthesis of ideas presented in his review is likely to have a big influence on future research. There are three good reviews on virus groups—J. B. Brooksby writes on foot-and-mouth disease, H. A. Wenner on the psittacosis group of viruses, and Ph. L'Héritier on the hereditary virus of drosophila. G. Bertani tackles an important topic—lysogeny—in a stimulating way. F. Fulton writes authoritatively on complement fixation as applied to virology, and Anne Buzzell and M. Hanig wrestle with influenza-virus hæmagglutination.

THE LANCET
LONDON 20 SEPTEMBER 1958

The Professional in Russia and China

IN our type of western society, professions are important. Even when most of their members are working in State organisations, the professions remain independent of Government and continue to set their own standard, exerting their corporate influence not only in their own interest but in that of the public, as they see it. As a rule, work is better done by people who belong to a profession, accepting its restraints and responding to its ideals; and the present tendency of vocational groups to demand professional status should be encouraged as part of the natural development of our kind of community. But there is also, of course, a contrary tendency towards denigration of professions as no longer necessary or useful for people who have entered a " State service ". Because of this, the professions could be seriously weakened even though structurally extant. There are warnings, perhaps, in the story of medicine in Soviet Russia, which has now well over 300,000 doctors but can be said to have hardly any medical profession at all.

In the book we review on p. 622 Dr. MARK FIELD, of Harvard, describes the social history of the Soviet medical profession as " the history of the transformation of a self-conscious, independent, vocal, politically oriented, and militant corporate entity to that of a docile and politically inert employee group ". The doctors of Tsarist Russia, " appalled by the poverty and the misery that surrounded them everywhere ", were many of them ardent reformers, and after the February revolution of 1917 they began to put into practice plans by which medical care and public health would be financed publicly but controlled and supervised by the profession. But in October all such projects came to an end with the advent of the Bolsheviks, whose philosophy could not tolerate the exercise of power or influence by anyone other than the State. Step by step, the new Government abolished the professional organisations and deprived doctors of their corporate strength by putting them into a vast Medical Workers' Trade Union in which (though they have a section of their own) they were swamped by feldshers, nurses, and other ancillary medical personnel. The ancillaries, having belonged to the formerly " exploited " classes, were now encouraged to assume the leadership formerly claimed by the bourgeois-liberal doctors. Moreover, the medical trade-union was itself subordinate to the central committee of trade-unions, and since the early '30s this has been hardly more than an instrument of the Government. " Little trace ", FIELD says, " was left of the medical profession as an organized, self-governing, social group or social force."

The " basic ethical universalism of medicine, which regards the sick individual as someone to be helped regardless of his station in life or class origins ", was displaced, in the new Soviet medicine, by a " class " approach: in medical care, as in housing, food, higher education, and other amenities, there was discrimination against people who were not party members or who did not belong to proletarian classes. Moreover, in a State which was on a war footing from its beginning, the interests of individual people came second to those of the community. Doctors should prevent disease; but, if they failed, they must at any rate do their utmost to prevent its interfering with production; and they were sometimes told that their first duty was to get as much work as possible out of their patients. Though this new sense of predominant duty to the community could scarcely be expected of people trained under the old regime, it was carefully inculcated into their successors, who now form the vast majority. Yet, strangely enough, the old medical tradition of personal service has survived. Despite official preference for workers' families, a high proportion of candidates for the medical schools come of middle-class parents who see in medicine a chance for their children to " help the people " without being directly involved with the regime or with politics.

Though no doubt most Russian doctors are generally in favour of the Socialist system which has modernised their country, FIELD produces evidence that less than a quarter are members of the Communist Party, and that most of these are administrators rather than clinicians. He speaks of a feeling among the others that party doctors " have somehow betrayed the profession by swearing allegiance to another group ". He was told of a " sharp social split between party and non-party physicians, and that the latter tried as much as possible to avoid contact and involvement with the former even in professional matters."

Especially in former days, when labour legislation was more draconian, doctors concerned with certification of illness were exposed to severe strains: the authorities often expected them to put industrial production before health, whereas the patients expected them to be merciful and be their friends. With a style and standard of living little above that of most of the population, the doctor tended to identify himself with the patient: and, as the " attorney of the poor ", he was often able, by judicious use of the medical excuse, to " cushion and somewhat soften the impact of the system on the individual ". Thus his work has become one of the adjustive mechanisms " that keep the social system going by reducing discontent, tension, and disaffection ". Though the regime regard it as potentially dangerous because it escapes control, it is willing within limits to let him exercise his adjustive functions; and in fact " the physician's role of certification is a latent source of strength and flexibility in the system ". It is an advantage to the regime that it has doctors who treat their patients as *their* patients—even at the risk of punishment. Similarly it is an advantage to the regime that, at the higher levels of medicine, some of the investigators have been less interested in official directives than in the progress of science outside their isolated country. There must be many who would agree with FIELD that " ideological controls imposed upon the medical pro-

fession add nothing to its efficiency, but rather detract from it by taking valuable time away from study and practice". Although (or perhaps because) there are no formal associations to band them together, there is a great deal of solidarity and cooperation among Russian doctors (other than party members); and now that political pressure on them has considerably abated, and international contacts seem rather easier, it will not be surprising if the profession regains some kind of corporate life.

Whereas differences between Soviet Russia and other industrial nations seem to be steadily diminishing, the same may not be true of China. The Russians began with a radically Communist revolution, but by successive concessions to expediency have achieved a national Socialist State now possibly in process of being liberalised. The Chinese, learning by Russian experience, began with many compromises but now appear to be moving towards a more fundamental reorganisation of their society. Among their compromises was the preservation of the Chinese Medical Association as the embodiment of the medical profession; and doctors from this and other countries who have visited China at the invitation of the Association have been heartened by finding that so many of its leading members have the same medical interests as themselves and apparently want to belong to the same medical world. On the other hand, even last year, the issue was evidently in the balance. The Chinese Medical Association has very close links with the Government, and official statements about the value of guidance by the Communist party have not been in line with FIELD's view (and ours) that "medicine, like other professions, is one in which the scientific approach must predominate and one which flourishes best in an atmosphere of free inquiry, scepticism, and the search for facts rather than doctrine, dogma, or political considerations". The Association's recent pronouncement on Anglo-American aggression in Arab countries [1] is depressing less because of its content than because it uses the stock phrases of Communist propaganda without so much as bothering to translate them into the more objective language more persuasive to doctors and scientists. Even several years ago, when he made the observations recorded on p. 633, Professor GOULD formed the impression that in the Chinese struggle between science and dogma, science had already been defeated; and there is now more reason to fear that he is right. If this fear is realised, however, we should still not make the mistake of underestimating what can be achieved by dogma, with technological aid; nor should we assume that what is thus achieved is necessarily inferior. One of the greatest sociological experiments of our time, if not of all time, is beginning with the Chinese Government's new programme for dividing their population into huge communes in which men and women alike are to form a labour force disposable between the tasks of agriculture and industry.[2] This scheme, which has the merit of avoiding the concentration of industry in cities with depopulation of the land, may take the Chinese much further towards Communism than the Russians have ever gone. Beside so vast a social change, the loss of a profession, of professional ideals, and of the scientific attitude may seem a small one. Nevertheless, in the long run, it would not be small at all.

1. *Chinese med. J.* August, 1958.
2. *Manchester Guardian*, Sept. 11, 1958, p. 1 and 7.

Fibrinolysin for Treatment of Blood-clots in Man

BLOOD-CLOTS are not permanent structures; they may serve as a supporting framework for invading fibroblasts and capillary blood-vessels, but as these form new tissue the clot of fibrin disappears. The process of getting rid of the fibrin—fibrinolysis—is now known to be brought about by a proteolytic enzyme and its precursors in blood tissues.[1] The active fibrinolysin is named "plasmin", and this is present in blood in an inactive form called "plasminogen"; plasminogen activators are present in blood, urine, and milk; trypsin can act as an activator. There is also a system of proactivators, and one of the best-known of these is streptokinase. Thromboembolism is still one of the serious causes of medical and surgical morbidity and mortality. Once a clot has appeared, we prescribe anticoagulants in the hope of preventing further clots, and this indeed is the basis of the anticoagulant treatment of coronary thrombosis.[2] But such treatment is like shutting the door after the horse has gone; tissue damage in the area blocked off by the original clot continues unchecked. It would be better if we could remove the clot or recanalise the vessel as soon as possible, in addition to preventing extension or complication. Accordingly attention has been given to fibrinolytic agents, and recent American reports suggest that a clinically useful fibrinolytic agent may have been prepared.

Streptokinase was tested as a fibrinolytic agent [3]; but streptokinase is not well tolerated and inhibitors were found commonly in blood. Intravenous trypsin has been given a trial [4]: it activates plasminogen and has some direct action on fibrin. But here again there were snags: antitryptic activity of plasma was found to be common; and the dose needed to produce an effect also interfered with other plasma-proteins, especially those concerned with blood coagulation. MOSER [5] has used a plasminogen prepared from the globulin fraction of human plasma-protein. The plasminogen is activated to plasmin by streptokinase, which is subsequently removed; this active plasmin does not attack plasma-proteins other than fibrinogen and fibrin. It had previously been shown [6] to remove clots produced experimentally in dogs and rabbits; and now MOSER has reported on its use in 52 cases of thromboembolic disease in man, including 13 of cerebral thrombosis. Lyophilised material was provided for clinical use, and it could be kept at −4°C for several months. It was assayed in "fibrinolytic units"; 1 F.U. is the amount of

1. Astrup, T. *Lancet*, 1956, ii, 565.
2. *ibid.* 1956, i, 559.
3. Tillett, W. S., Johnson, A. J., McCarty, W. R. *J. clin. Invest.* 1955, **34**, 169.
4. Taylor, A., Overman, R. S., Wright, I. S. *J. Amer. med. Ass.* 1954, **155**, 347.
5. Moser, K. M. *ibid.* 1958, **167**, 1695.
6. Grossi, C. E., Clifton, E. E. *Surgery*, 1955, **37**, 794.

preparation which will change the turbidity of a standard fibrinogen-thrombin clot by 50% in ten minutes. Clinical doses varied from 30,000 F.U. to 90,000 F.U., the dose being increased as experience confirmed the safety of the substance; the lyophilised material was dissolved in 500–1000 ml. of 5% dextrose solution and infused over two to four hours. This material nearly always provoked a febrile reaction six to eight hours after the infusion, but any symptoms could be ameliorated by giving an anti-histamine drug; there was 1 case of generalised urticaria and 1 of local erythema. There was no effect of any of the blood-coagulation tests. Plasma-fibrinogen estimations showed that a small loss had occurred six hours after a dose of plasmin, but values were normal again in twenty-four hours. There were no hæmorrhages even in patients having anticoagulant treatment. The fibrinolytic activity of the patient's plasma reached a maximum three hours after an infusion of plasmin; 30,000–50,000 F.U. raised the activity by 30%, and 70,000–90,000 F.U. produced a rise of 40%.

The best results were obtained with peripheral venous thrombophlebitis and pulmonary embolism. 18 patients with deep venous thrombophlebitis were treated; most of them showed loss of heat and tenderness and decreased swelling within twenty-four hours, and within seventy-two hours the affected part returned to normal; the phlebitis did not recur when the patient got out of bed, and pulmonary embolism did not occur after the treatment. Experience with 12 cases of peripheral arterial occlusion was less encouraging; no patient was certainly relieved. Of 14 patients with cerebral arterial occlusion there was maintained improvement in 4, transient improvement in 3, and no effect in 7; MOSER considers that from this small group no definite conclusions can be reached, but there was no evidence that any patient deteriorated, and the infusions could be given with safety. In coronary thrombosis not enough patients have yet been treated to decide whether fibrinolysin will be useful. SUSSMAN and FITCH [7] used the same preparation of plasmin as MOSER for the treatment of 3 patients with cerebral arterial occlusion. In 1, with occlusion of an anterior cerebral artery, there was no effect. In another, aged 75, with hypertension, a left carotid arteriogram showed occlusion of the internal carotid artery just beyond the bifurcation of the common carotid artery; infusions of plasmin into the left carotid artery produced some clearing, but there was no clinical improvement. In the 3rd patient, who had occlusion of the middle cerebral artery, the block was relieved after plasmin infusions and there was some clinical improvement.

These results suggest that it is worth obtaining further experience with plasmin preparations, especially in the treatment of superficial and deep thromboses of leg veins. The results in cerebral vascular disease have so far been disappointing, but in this group of disorders we have so little effective treatment that even not very promising methods are worth testing. We still need more information on toxicity and on dosage; and we need to know whether fibrinolysin treatment should be followed by anticoagulant treatment, and for how long. The American workers used a plasmin preparation that was commercially available, and it should not be difficult for a similar preparation to be made in this country.

7. Sussman, B. J., Fitch, T. S. P. *J. Amer. med. Ass.* 1958, **167**, 1705.

Decline of the Father-image

THE increase in crime during the past few months is worrying everyone, and rightly so, for, however critical one may be of Home Office statistics, the present crime-wave must be accepted as real and disquieting. Yet its cause remains as obscure as the cause of crime itself. From a psychological standpoint, it is easy to agree that a defect in the super-ego plays a large part in inducing criminal behaviour, and to accept FREUD's thesis that the super-ego is formed by parental and other authority, and is the repository of morals, prohibitions, conscience —in fact, of the sense of right and wrong. But it is less easy to define the super-ego precisely, and still harder to pick out the influences which determine its function for better or for worse.

Recent studies of this problem include two investigations using the thematic apperception test and have provided some tentative information. (The test consists in asking the subject to tell a story round each of a series of pictures showing situations of differing emotional flavour.) In Australia LYLE and GILCHRIST [1] compared the results it gave in groups of delinquent and normal boys, and in the United States JENSEN [2] applied it to groups of boys showing extremes of aggression and passivity. The amount of aggression shown by all the boys did not greatly differ, but delinquent and aggressively antisocial boys related stories of "naked" aggression, whereas the normal and the passive groups "buffered" their fantasies of violence with just retribution, suicide of the malefactor, and mitigating factors such as stealing for a starving family or acting under hypnosis. Analysis of stories according to some other criteria showed, surprisingly, no significant differences among the groups. Thus references to murder, robbery, intra-family tensions, feelings of rejection, love, and loyalty, were evenly distributed between the groups. But socially taboo aspects of sex, violence, and language were more common in the stories of the antisocial boys. The difference between the groups was not in aggressiveness itself, but in their social attitude towards it: the antisocial groups showed a lack of guilt-reaction—a defect, in fact, of the super-ego.

These studies still leave open the reasons for this psychological defect, and people tend to put forward unverified suggestions which vary according to the ethical, religious, social, or political tub which they happen to be thumping. But the reasons lately put forward by GALDSTON [3] deserve careful consideration. He lays the blame on the decline of the family, and particularly the change of orientation within it. Writing of the United States, he describes the cult of "momism" and suggests that American society has swung from a pat-

1. Lyle, J. G., Gilchrist, A. A. *Brit. J. med. Psychol.* January, 1958, p. 51.
2. Jensen, A. R. *Psychol. Monogr.* 1957, **71**, 13.
3. Galdston, I. *Ment. Hyg.* 1958, **42**, 229.

riarchal to a " matriarchoid " pattern—if we may hesitatingly use his neologism. Modern technology and social circumstances have emancipated the mother to the point where she no longer needs to bake the bread, weave the cloth, feed the chickens, and teach the children, nor does she (as the father must) earn the money. She is free to build up a dominating position within the family, and to wreak havoc on the children by overprotecting them and ousting father as the principal figure. As he says:

> " The patriarchal family is rapidly disintegrating and in that process we are experiencing and witnessing a negation of those patterns, values and mores on which and by which our multi-millenial culture has been structured and buttressed . . . Freud has taught us that the super-ego represents the introjected or incorporated father-image. In the matriarchal family there is no conscionable father-image to introject."

GALDSTON's views on the matriarchy have some support from the GLUECKS' findings [4] that fathers of delinquents tend to be incompetent and lax in discipline. Nearer home, the Metropolitan Police Commissioner [5] has reported a rise of 30%, during 1957, in young offenders between the ages of 17 and 21—many of whom, as war children, must have lacked even an incompetent father. Those who agree with GALDSTON's observation that the structure of the family is changing may nevertheless be more cautious in laying responsibility for the change on the leisured mother. During the Victorian age, for instance, thanks to maids rather than washing-machines, mothers of the middle classes probably had at least as much leisure as the mothers of today. Yet paterfamilias retained his position as undisputed head of the family.

However debatable this may be, few would disagree with GALDSTON when he points out that in the past the family was not merely a conglomeration of people but a working union. Nowadays many of its duties and responsibilities have been taken over by other organisations, and the services for which the members of a family used to rely on each other have been reduced almost to vanishing-point. Children, he reminds us, used to be an asset and from early years had their own useful place within the family. But now they are regarded as a luxury, to be indulged in circumspectly. They have no useful place, especially in urban life, and, save for their school work, have little to do and that little is of a "make-work" character.

Nor does he neglect the importance of religion, surely the most super of super-ego forces. The Church, he points out, was once the centre of art and culture, of music and community gatherings, of the healing and social services.

> " Man is a creature that lives by values no less than by bread, and of late too many of his traditional values have been cast into doubt. In the cataclysmic upheavals of two world wars, goodness, love, charity, mercy, truth, humility, brotherliness, have been violated and mocked. There is current a highly organised, energetic and cunningly resourceful propaganda which makes the homely virtues and the religious persuasions and faiths of our fathers appear like a compound of neurotic anxiety, infantile delusions, political-economic naivété and mean escapism. Many who are caught in the tension field of this propaganda seek refuge in doctrinate bigotry; hence the resurgence of orthodoxy in morals and religion."

Much has been written about the so-called sick society (was it ever healthy?), and surely there can be no simple answer to the complex troubles of a complex civilisation. Admittedly GALDSTON begs many questions. (Would he, for instance, call English society matriarchoid?) But challenging views such as his are needed, if only to stimulate further social and anthropological studies. A careful examination of the patient has long been held to be a useful prelude to effective treatment.

4. Glueck, S., Glueck, E. Unraveling Juvenile Delinquency. New York, 1950.
5. Annual Report of the Metropolitan Police Commissioner, 1957. H.M. Stationery Office.

Annotations

FAMILY DOCTORS AT WORK

SINCE 1948 a great many words have been spoken and written about general practice under the National Health Service; many of them, perhaps too many, have suggested that the standard of care is deteriorating and have depicted the general practitioner himself as overworked, underpaid, and ill-supported in his work. When the present is difficult it is tempting and natural to recall the past with indulgence and regret; but in its day the past probably had its difficulties too, and before accepting criticisms of general practice it is worth considering how many are founded on opinion and how many on fact.

Prof. R. M. Titmuss, who takes a reasonably optimistic view of the family doctor's opportunities and progress within the administrative framework of the N.H.S., reminds us that some of its keenest critics have failed to make explicit the criteria they have in mind, and have avoided concrete comparisons with the conditions of the 'thirties. Expressions of opinion are never easy to rebut, especially when there are few facts with which to challenge them. Statistics and controlled observations about general practice are scanty and incomplete; but such as they are, in Professor Titmuss' view, they offer little support to the critics. He has summarised the 15 available surveys in a useful appendix to his stimulating American lectures, which have now been published in this country.[1] The most reliable evidence in his view comes from figures collected by the Ministry of Health and the British Medical Association, and according to them the quantity of the family doctor's work has not increased since the 'thirties. In 1938–39 he gave each of his panel patients 5·10 items of service; in 1949–50 he gave each of his N.H.S. patients 4·62 items. These figures do not suggest that patients are making unreasonable demands on their doctors. Indeed N.H.S. patients might reasonably be expected to have needed more items of service, for, unlike the panel patients, they include vulnerable groups of children and old people; yet the number of items has actually fallen. There are, however, no figures for the demands of private patients, and since the introduction of the N.H.S. some of these are probably turning to their doctor more freely. Among these patients the doctor's work may have increased. Even so Professor Titmuss considers that the level of total demand has remained relatively low.

In other ways he thinks that the doctor's work has been lightened. The doctor is making more use of

1. Essays on " The Welfare State ". London: George Allen & Unwin. 1958. Pp. 232. 20s.

hospital outpatient facilities, and of the services of district nurses for injections and dressings. Doctors are also more evenly distributed over the country, many have arranged voluntary rotas, and night visiting is becoming rarer. Nor does the N.H.S. patient seem to need as many certificates as some suppose (48 per 100 N.H.S. patients in 1953–54, compared with 139 per 100 panel patients in 1938–39).

Quality is more difficult to assess than quantity, and standards of general practice cannot be judged on even the tenuous objective evidence available for quantity. But here, too, Professor Titmuss is unimpressed by over-facile jeremiads. The figures put before the Spens Committee, he reminds us, show that in the 'thirties too many practitioners were earning a miserable income, and in his view private practice was "less remunerative than most people were aware of then or imagine today". Most practices carried a burden of bad debts, and too many patients, oppressed by the cost, were reluctant to seek their doctor's help. Excellent as general practice often was, its benefits were often limited by accidents of wealth or locality, and families living in an industrial slum did not enjoy the same benefit as a family living in the village of Aysgarth.

His more buoyant assessment of general practice does not, however, mean that Professor Titmuss does not appreciate the problems that beset general practitioners today. He lays responsibility for many of these, however, not on the N.H.S., but on the impact of the physical sciences on medicine during the past forty years or so, and the increasing specialisation which these new complex techniques have demanded. Before 1948, Professor Titmuss points out, the general practitioner was usually a "singlehanded, professionally isolated, private entrepreneur". The more isolated the institution the greater the tenacity of custom and tradition, and Professor Titmuss suggests that his past isolation is partly the cause of the general practitioner's difficulty in adjusting himself easily to the swift technical changes in medicine and in accepting the necessity for greater reliance on the help of his colleagues.

Divided skills have unfortunately, but perhaps not unnaturally, brought divided loyalties, and Professor Titmuss would admit that these have been accentuated by the N.H.S., which has tended to centre the consultant services on the hospitals and to deprive the general practitioner of his place as the ultimate source of consultant practice. But if some aspects of the N.H.S. and of specialisation have tended to divide the profession and medicine, by fostering group practice and teamwork they are also potentially cohesive influences. Science has already offered the general practitioner effective new drugs, such as the antibiotics, which he can use in his own practice. The National Health Service has not only offered his patients care in hospital: it has also promoted the domiciliary services with whose help he can treat more of his patients in their homes. His growing preoccupation with early mental disease offers him new scope in preventive medicine. But these changes, though offering him new opportunities and more effective means of treatment, have destroyed some of his reliance on his personal interpretation of clinical experience, just as the growing knowledge and expectations of his patients have deprived him of some of his traditional unquestioned authority.

The National Health Service by providing an official whipping-boy has enfranchised complaints—from doctors and patients alike. But, as Professor Titmuss points out, many of these complaints are also made against private practice in the United States. In his view the true target is the changes in practice and the shifts in emphasis caused by "the eruption of science into medicine". The National Health Service is not responsible for these changes, and indeed in many ways is helping medical practice to assimilate them by providing a framework "through which medicine may more nearly fulfil its honoured purpose; the means by which the freedom of doctor and patient alike may be enlarged".

CORTISONE AND RECURRENT POLYNEUROPATHY

THERE is suggestive but not conclusive clinical evidence that in acute infective polyneuropathy of Guillain-Barré type cortisone may stop the rapid deterioration and may hasten recovery once deterioration has been stopped.[1 2] Austin,[3] of the University of Oregon, has described a remarkable case of recurrent polyneuropathy which indicates clearly that corticotrophin and cortisone were of value in treatment. A number of cases of recurrent polyneuropathy of unknown ætiology have been recorded since the first description by Targowla in 1894.[4] Typically the patient is a young adult who over many weeks or months develops a symmetrical, chiefly motor and distal, polyneuropathy, possibly with cranial-nerve involvement and an increased content of protein in the cerebrospinal fluid. Disability is greatest after four to five months, and the patient then begins to improve slowly and often recovers completely. After months or years of normal health a second attack occurs. In the 32 recorded cases reviewed by Austin the average number of attacks was three, and 4 patients died during an attack

Austin's patient was a man, aged 40, who in five years had twenty attacks of polyneuropathy, and extensive investigation did not reveal the cause. The first attack became steadily worse for eight months; intramuscular corticotrophin halted the progress of the disease; this was followed by intravenous corticotrophin; improvement started within three days, and in two months he was without symptoms and was back at work. After being well for eleven months he had a similar attack with slow deterioration, and after three months he was severely disabled. Deterioration continued when he was given intravenous infusions of glucose and water as a placebo, but improvement started on the fourth day on which he was given an intravenous infusion containing corticotrophin. Studying this patient's recurrent attacks over five years, Austin found that there was a consistent, reproducible, and predictable pattern of response to corticotrophin, cortisone, prednisone, and placebos. Improvement began after the hormones were first given or the dosage was increased; bouts began after dosage was reduced, and on each of three occasions significant deterioration occurred during oral, intramuscular, or intravenous administration of placebos. There was a definite time-lag between the start of hormone administration and clinical improvement; this usually varied from five to seven days—a longer lag than in the acute symmetrical polyneuropathies, where two to three days is usual.

In this unique case the value of hormone treatment is clear; but, as Austin says, the hormones temporarily suppress clinical manifestations when the neuropathy is

1. Graveson, J. S. *Lancet*, 1957, i, 340.
2. Jackson, R. H., Miller, H., Shapira, K. *Brit. med. J.* 1957, i, 480.
3. Austin, J. H. *Brain*, 1958, 81, 157.
4. Targowla, J. *Rev. neurol.* 1894, 2, 465.

active but do not cure the disease, and the patient now appears to be having continuous hormone treatment. The mechanism by which cortisone acts in this case is by no means clear. In 11 of the 32 reported cases of recurrent polyneuropathy that are reviewed, clinical enlargement of peripheral nerves was recorded. In this patient's first two episodes, when there was a delay of three months or more before hormones were administered, enlarged firm nerves were felt; but in the later bouts, when hormones were given in the early stages, there was no clinical enlargement. Biopsy of the left sural nerve in the second bout three weeks after corticotrophin had been started showed mild to moderate interstitial and subperineural œdema. Austin does not consider that the dysfunction in the peripheral neurones was due to a compressive effect of this interstitial œdema, and he suggests that the œdema is due to distended capillary and cell-membrane permeability and that this might seriously affect fluid-electrolyte distribution and other metabolic functions of the axone-myelin-Schwann cell complex with resulting impairment of function.

ESCHERICHIA COLI IN FARM ANIMALS

Escherichia coli was long suspected in an indeterminate way of causing diarrhœal diseases in man and animals, but conviction had to await the work of Kauffmann in subdividing this universal species into types or subspecies by serological methods. It is now well known that some of these types may be associated with acute diarrhœa in infants: both the clinical picture and the pathological changes in bowel and kidneys are fairly characteristic. The evidence that these types are the " cause " (in the sense that *Salmonella typhi* is the cause of enteric fever) is suggestive. The organism is present in the bowel at the acute stage of the disease in almost pure culture, and it disappears in convalescence. The disease produces specific antibodies in the blood and has been reproduced experimentally. In certain children's hospitals the disease has behaved as an extremely infectious specific fever, and methods of control based on this thesis have had some moderate success. The pathogenic types of *Esch. coli* have, however, been found quite frequently not only in adults but in healthy infants congregated in institutions. An epidemic is due to a single type, but within an institution this type may for no obvious reason disappear or be replaced by another type. Some types (e.g., 0·111 B.4) which did most damage ten years ago are nowadays almost extinct.

Certain serological types of *Esch. coli* have been identified as the cause of scours in calves, and, as in man, the types responsible have changed over a period of years. (With one or two exceptions the types pathogenic to calves have so far been harmless to infants). Because calves can be observed experimentally, we know rather more about the epidemiology of their disease [1] than that in babies. Maternal antibodies transmitted in the colostrum normally give a high degree of protection, but if the calf is brought into contact with pathogenic types of *Esch. coli* antibodies to which are not present in the colostrum it will probably die. This is borne out in practice by the experience that it is unwise to move a calf to a fresh environment in the first few days of life or even to move the cow shortly before the calf is born. The protection given by colostral antibodies is not absolute: an overwhelming infection by a virulent type will sometimes swamp the defences.

1. Lovell, R. *Vet. Rev. Annotations*, 1955, **1**, 1.

" Gut œdema " has been known for many years as a serious disease of pigs, and is usually ascribed to dietary indiscretion. The name is apt, but the œdema may affect other parts: postmortem appearances are not unlike those in some cases of " coli enteritis " in infants. New light has been thrown on the ætiology of this disease by the observation that in almost every case *Esch. coli* of one of four specific serological types are present in the bowel and mesenteric glands, and that the disease can be reproduced by the intravenous injection of an extract of one of these types.[2] There is also some evidence that a specific antiserum may benefit some infected animals. Of the epidemiology of this disease we are still rather ignorant. Most commonly it attacks store pigs of 10–14 weeks but it may occur in younger animals. It does not seem to have the characters of an acutely infectious fever, but traditionally its onset follows a change of housing or of diet. To confuse the inquiring veterinarian there arises in young piglets an apparently distinct diarrhœal disease which seems to be akin to scours in calves; the types of *Esch. coli* responsible for this are distinct from those associated with gut œdema.

These diseases of man and animals have many likenesses but also some obvious differences. In each case there are reasonable grounds for believing that the observed pathological changes are due to toxins produced by specific types of *Esch. coli*. (Although one or two of the types causing scours have been found in infants it is generally true that each disease is associated with its peculiar specific types). It also seems clear that the types which cause infantile enteritis and scours are not invariably pathogenic. In this connection Lovell has suggested that the soil is as important as the seed, and by his own work has demonstrated the importance of immunity acquired from the mother. Babies, of course, get their maternal antibodies through the placenta; and there is no evidence, so far as we know, that these play any part in protecting the infant against enteritis due to *Esch. coli*. A change of environment (which means, probably, contact with alien types of *Esch. coli*.) seems to be of real importance in precipitating these diseases among animals. Its danger in man is less easy to establish. Because we live in relatively isolated families, diarrhœal diseases of infants are likely to be seen in epidemic form mainly in institutions; but, in fact, single infections in the home and in the communal nursery are not uncommon.

There is one other factor which tangles further an unruly skein. Beyond much doubt there are diarrhœal diseases of man and animals due to filterable agents.[3,4] In man these are highly infectious but less severe than those due to *Esch. coli*. On the analogy of hog cholera, a viral disease almost always complicated by infection with *Salmonella choleræ-suis*, the suggestion has been made that all these enteric diseases of young animals are primarily due to infection with one or more viruses but are complicated and perhaps made more severe by the specific types of *Esch. coli*.

These diseases are receiving much attention, and on economic grounds alone they deserve it. Our knowledge of the comparative morbid anatomy is scanty. Observations in the field and the hospital have been often disjointed and unplanned. The methods of experimental epidemiology which have been so fruitful in the calf can be applied to pigs and even, in part, to man.

2. Sojka, W. J., Erskine, R. G., Lloyd, M. K. *Vet. Rec.* 1957, **69**, 293.
3. Brandly, C. A., McClurkin, A. W. *Ann. N.Y. Acad. Sci.* 1956, **66**, 181.
4. Hodes, H. L. *ibid.* p. 215.

Special Articles

MINAMATA DISEASE
AN UNUSUAL NEUROLOGICAL DISORDER CAUSED BY CONTAMINATED FISH

DOUGLAS MCALPINE *
M.D. Glasg., F.R.C.P.
SHUKURO ARAKI
M.D. Kumamoto
From the Department of Neuropsychiatry, the Medical School, Kumamoto University, Kyushu, Japan

Minamata is a small industrial town near the south-west coast of Kyushu, the most southerly of the main Japanese islands. The chief industry is provided by a large artificial-fertiliser factory, the effluent from which empties into Minamata Bay. A number of villages are located on or near this bay, mainly to the north and the south. The short coastline opposite the middle of the bay is uninhabited (see figure).

From the end of 1953 a mysterious nervous illness began to affect the villagers near the bay, and by 1956 it had assumed epidemic proportions. The outbreak was investigated by a number of departments of Kumamoto University and the results were published last year in the *Kumamoto Medical Journal* (Kitamura et al. 1957).

Clinical Features

During 1956, 15 cases (9 adults and 6 children) were admitted to Kumamoto University Hospital.

The onset of illness was acute or subacute and usually unattended by fever or constitutional symptoms. In all the adults numbness developed in the extremities and sometimes around the mouth, often accompanied or followed by slurred speech, unsteady gait, and increasing disability. Most of the patients complained of deafness and disturbance of vision, the latter being associated with generalised constriction of the fields. Dysphagia and increased salivation were less commonly observed. Insomnia was a striking feature in 3 adults and 2 children. 6 adults showed emotional lability in the form of euphoria or depression. The seriously ill patients were mentally confused; drowsiness and stupor alternated with periods of restlessness and shouting. Cerebellar ataxia and dysarthria were always present, but nystagmus was noted in only 1 patient. Choreiform or athetotic movements were observed in several adults, and hemiballismus in 1. The deep reflexes were exaggerated in 4 patients and depressed in 2; an extensor plantar response was noted twice. Distal hypæsthesia was found in the limbs of 3 adults, but in reports no mention was made of vibration or postural senses. Epileptiform attacks occurred in 1 child and 1 adult during the period of observation.

4 adults showed a mild degree of secondary anæmia. The cerebrospinal fluid was normal except for a moderate pleocytosis in 1 patient. The serum showed an increase of gamma-globulin. An abnormal amount of aminoacids was found in the urine of the more seriously ill adult patients. Estimation of serum-copper was normal; manganese was found in excess in 1 case.

The course of the disease fluctuated and its results were variable; the most severely affected died, while others remained incapacitated in varying degree. Improvement in hospital was occasionally followed by relapse on returning home.

Pathology

The brain and certain internal organs from 4 patients, and one spinal cord, were available for study.

Apart from small areas of necrosis in the intestinal mucous membrane, and scattered areas of necrosis in the liver in 1 case, there was no abnormality of the viscera. The main findings in the central nervous system were: (1) cell degeneration, which was most marked in the granular layer of the cerebellum, while changes of varying degree were apparent in the basal ganglia, hypothalamus, midbrain, and cortex; (2) dilatation of the perivascular spaces, with occasional softening, but no true demyelination; (3) œdema and occasional small hæmorrhages; and (4) reactive gliosis. The spinal cord showed minor changes; the anterior-horn cells were unaffected.

Epidemiology

The public-health department of Kumamoto University reported 52 patients, all of whom frequently ate fish from Minamata Bay. There were 39 cases in four villages with a total population of 2091, giving a morbidity-rate of 19 per 1000 population. The remaining 13 were scattered over seven districts with a population of 7988, giving an overall rate of about 5 per 1000.

The figure shows that with one exception, namely a barber living on the outskirts of Minamata Town who fished in his spare time, all the cases occurred in the neighbourhood of the bay. The patients were distributed among 40 families. In 36 (90%) of these at least one member fished in the bay, but in 48 (71%) of 68 neighbouring families who were unaffected no-one fished. 25 of the 40 affected families every day ate fish or shellfish which came from the bay, and the remaining 15 consumed fish from the bay two or three times a week. By contrast, only 5 of the 68 unaffected families were in the habit of eating fish daily from the bay, and most of them ate less fish per week than the affected families. Of 31 males and 21 females who became ill, 10 were children under the age of ten, but no infants were affected. By December, 1956, a further 4 cases had been reported. Of the original 52 patients, only 3 were able to return to work within 6 months, 9 improved, and 23 were stationary; there were 17 deaths. This gave a case-mortality of 33%. 8 patients died within 2 months and 4 within a year.

* Present address: Institute of Clinical Research, Middlesex Hospital, London, W.1.

Based on a map published by the public-health department of Kumamoto University to illustrate the distribution of 52 cases of Minamata disease.

Fishing in Minamata Bay was mainly carried out at night; on returning home in the morning the fishermen and their families usually ate raw the freshly caught fish. But the survey of the public-health department showed that cooked as well as raw fish can cause the disease, which suggests that the toxic substance is thermostable. Those who ate fish for breakfast seemed likely to consume more daily than the school-children who left home before the morning catch had been brought in; this may account for the escape of several children of families in which other members were affected.

A Disease in Animals

A disease also appeared in animals which had eaten fish or shellfish.

In the 40 affected families there were 61 cats and 50 died between 1953 and 1956, sometimes in as little as 2 days. Unsteadiness, frequent falls, circling movements, and convulsions were observed; forced running appears to have caused some of them to enter the sea and be drowned. The 68 unaffected families owned 60 cats and of these 24 died. 5 pigs and 1 dog died, also many crows which were in the habit of settling on a floating landing-stage where the returning fishermen tied up. The brains of 10 cats were examined; the changes were similar to those observed in the human material, the granular layer of the cerebellum being especially affected. The disease could be readily produced experimentally in cats by feeding them for 2 to 4 weeks with fish from Minamata Bay.

Chemical Investigations

The chemical investigations were difficult to evaluate since several departments carried out independent analyses of human and cat material, and of fish from the bay, with varying results, but the following appear relevant:

(1) Some fish and shellfish from the bay showed increased amounts of manganese, selenium, and copper as compared with controls from another area, while the amounts of thallium, arsenic, lead, and iron were not significantly raised.

(2) The silt from that part of the bay into which the effluent from the fertiliser factory flowed was dark in colour, mud-like in consistence, and contained sulphur and a toxic sulphur derivative, mercaptan (ethane-thiol). Large amounts of selenium, and smaller amounts of manganese, thallium, copper, lead, and iron were also found in the silt; all were increased as compared with the analysis of sand from another part of the coast.

(3) Selenium was present in human and cat livers in roughly the same proportion as reported in cases of selenium intoxication, and manganese was found in the hair of the affected cats.

(4) The raw material used by the factory contained, inter alia, thallium and selenium.

(5) In 1953 the principal products of the factory were ammonium sulphate, ammonium and calcium phosphate, sulphuric acid, carbide, and nylon.

It was concluded that the outbreak had been caused by a toxic factor in fish but there was no agreement as to its nature.

Personal Observations

During two visits to Minamata in February and March, 1958, we had the opportunity of examining 16 patients in their homes, and 6 others in Kumamoto University Hospital.

Multiple cases occurred in 3 families:

Egoshita family.—During 1956 both parents and 2 sons (aged eleven and nine) noticed mild peripheral numbness, dysarthria, and ataxia, but they all gradually recovered over a period of several months; a daughter (aged five) developed dysphagia in addition, and died in hospital of aspiration pneumonia. 1 other older son living at home was not affected.

Kaneko family.—The father became ill with dysarthria, tremor, and ataxia during 1954; his condition slowly deteriorated and he died in June, 1955. Also during 1954, the elder son (aged five) developed similar symptoms associated with spastic weakness of the left leg, but he gradually improved after a few months. The younger son had a severe attack of measles in 1956, when eight months old, and afterwards failed to sit up, talk, or walk. But he was entirely breast-fed until after the age of two—which makes the diagnosis of Minamata disease unlikely, since the mother remained well throughout.

Tanaka family.—In March, 1956, a child of six was febrile for 1 day, and during the next 2 or 3 weeks developed progressive ataxia, dysarthria, dysphagia, and visual deterioration. In April she became agitated and had a generalised convulsion; nasal feeding was necessary and she was admitted to hospital. In February, 1958, she was mute, deaf, and apparently mentally defective. She could not sit up though she was able to see large objects. The pupils and fundi were normal; all four limbs were flexed and spastic. A younger sister (aged three) developed progressive dysarthria and ataxia in April, 1956, and later dysphagia and incontinence. When seen by us she was mute and unable to sit up, though she could move all her limbs freely. The optic discs were normal, the deep reflexes were exaggerated, and the plantar responses equivocal. The mother was normal, but no details are available of the rest of the family. (The history of these 2 sisters was taken from notes published in the *Kumamoto Medical Journal*—pædiatric department, cases 1 and 6—in 1957.)

Discussion

The salient facts regarding this unusual outbreak seem reasonably clear. In a scattered community, living near the sea, there appeared an obscure neurological illness which assumed epidemic proportions within 2 years, causing death in more than a third of its victims and serious disability in most of those who survived. Concurrently, a fatal illness affected domestic animals and also scavenging crows and fish in a nearby bay. Two facts were established—firstly, that there existed a close relationship between the eating of fish and the occurrence of the disease, and, secondly, that the fish responsible for the outbreak had been caught in Minamata Bay. This last observation was supported by the results of a ban placed on fishing in the bay which came into operation in November, 1956, since when no fresh case has been reported. Chemical analysis of silt from the bay suggested that the water was polluted by effluent from a fertiliser factory. Inquiry showed that the factory introduced no new process in 3 years before the outbreak. Professor Kitamura, however, pointed out that until 1950 the effluent was diverted into the open sea by a channel to the north of the factory, but in 1950 this was closed and a new one constructed which runs directly to Minamata Bay (see figure).

Clinically, the subacute onset of numbness in the distal portion of the limbs and occasionally around the mouth suggested peripheral nerve involvement. In a few patients the numbness became generalised and was accompanied by sensory ataxia, recalling the so-called "sensory neuropathy", in which posterior-root ganglia are primarily affected, usually as a complication of carcinoma (Denny-Brown 1948, Henson, Russell, and Wilkinson 1954). Cerebellar symptoms were conspicuous at the onset but nystagmus was a rare finding. Not infrequently there was deafness and disturbance of vision; in the few cases in which perimetry was performed the visual fields were generally constricted. With one exception, the optic discs were normal in patients examined 2 or 3 years after the onset. Pyramidal signs were occasionally found. In the more seriously ill patients

there were symptoms of an encephalopathy—i.e., mental confusion, stupor or coma (in the fatal cases), convulsions, involuntary movements of varying type, and insomnia. In some, the presence of intellectual deterioration, mutism, epilepsy of late onset, an increasing degree of limb spasticity, and incontinence suggested a form of progressive neuronal degeneration. Involuntary movements were occasionally prominent in the early stages, but we did not observe parkinsonism or choreoathetosis as a sequel, though, in one case, there was a striking tremor of the red nucleus type.

There seems to be a fair measure of agreement between the clinical and pathological findings as to the anatomical localisation of the disease, but the ætiological factor is uncertain. In the published reports on Minamata disease no mention is made of gastrointestinal symptoms, but the possibility that a toxic metallic compound was responsible for the outbreak is supported by the occasional complaint of increased salivation and by the finding of areas of intestinal necrosis in each of the 4 patients who came to necropsy.

Some of the neurological features of Minamata disease have been observed in toxic states due to certain metals.

Methyl mercury compounds may cause ataxia, dysarthria, constriction of the visual fields, an occasional extensor plantar response, and, experimentally, peripheral neuritis and degeneration in the granular layer of the cerebellum (Hunter, Bomford, and Russell 1940). Thallium may cause a complex neurological picture—i.e., psychosis, choreiform movements, inversion of sleep rhythm, deafness, retrobulbar neuritis with optic atrophy, ocular pareses, bulbar palsy, pyramidal signs, and peripheral neuritis. In severe cases convulsions may be followed by coma and death (Prick, Smitt, and Muller 1955). In carbon-disulphide intoxication manic-depressive psychosis and mental confusion may be prominent, while peripheral neuritis, disturbance of vision, optic atrophy, deafness, and, in the chronic stage, parkinsonism may occur. Manganese mainly affects the basal ganglia, resulting in a variety of striatal symptoms, including parkinsonism. Mild psychiatric symptoms have been attributed to chronic intoxication with selenium (Lemley and Merryman 1941), but we have been unable to find reference to neurological manifestations.

Degeneration in the granular layer of the cerebellum, a conspicuous feature of Minamata disease, is non-specific, having been found in various pathological conditions such as anoxia, hyperglycæmia, hypoglycæmia, mercury intoxication (bichloride and methyl compounds), and chronic alcoholism (Leigh and Meyer 1949, Neuberger 1957).

Of the three metals manganese, selenium, and thallium, which have received most attention from those investigating the disease, only the last-named seems likely to produce on the nervous system an effect similar to Minamata disease. It is hoped that the results of work which continues in Kumamoto University may throw light on the nature of the toxic agent responsible for this unusual outbreak.

Summary

The clinical, pathological, and epidemiological features are described of an unusual neurological illness which, between 1953 and 1956, attacked villagers living near Minamata Bay in Kyushu Island, Japan.

Characteristically the disease affects the peripheral nervous system, the cerebellum, hearing and vision, and less frequently the pyramidal tracts. In severe cases an encephalopathy may be followed by signs suggesting progressive brain damage.

The pathological findings are widespread neuronal degeneration, particularly in the granular layer of the cerebellum, and areas of intestinal necrosis.

Fishermen and their families were mainly affected and the evidence suggests that the disease was caused by eating fish caught in Minamata Bay.

Concurrently a disease associated with ataxia and convulsions proved fatal among domestic animals, especially those belonging to affected families, and also among scavenging crows.

Although the cause is not yet established, the evidence so far points to the toxic action of an inorganic chemical compound contained in the effluent which flowed into Minamata Bay from a nearby fertiliser factory.

We would like to acknowledge grants received from the National Institute for Neurological Diseases and Blindness, Bethesda, 14, Maryland, and to thank Prof. R. Myagawa who afforded us facilities for this study.

REFERENCES

Denny-Brown, D. (1948) *J. Neurol. Psychiat.* **2**, 73.
Henson, R. A., Russell, D. S., Wilkinson, M. (1954) *Brain*, **11**, 82.
Hunter, D., Bomford, R. R., Russell, D. S. (1940) *Quart. J. Med.* **33**, 193.
Kitamura, S.; Katsuki, S.; Kawamori, Y.; Tokuomi, H.; Nagano, S.; Osaki, M.; Seben, E.; Takeuchi, T.; Rokutanda, G.; Irukayama, K.; Sera, K.* (1957) *Kumamoto med. J.* (Suppl., January and June).
Leigh, A. D., Meyer, A. (1949) *J. Neurol. Psychiat.* **12**, 287.
Lemley, R. E., Merryman, M. P. (1941) *Journal Lancet*, **61**, 435.
Neuberger, K. T. (1957) *Arch. Path. (Lab. Med.)*, **63**, 1.
Prick, J. J. G., Smitt, W. G. St, Muller, L. (1955) Thallium Poisoning. Amsterdam.

* Owing to the large number of authors only the names of principals are given.

U F A W

(The Universities Federation for Animal Welfare)

THE medical profession exists for a purpose which is essentially humanitarian, and the humane mentality which belongs to it may be expected to extend beyond the human species to the other animals, which are, so to speak, man's poor relations. But the practical expression of this interspecific sympathy, which is a logical development of man's intraspecific social conscience, has been hindered during the past three-quarters of a century by the controversy about vivisection, and in lesser degree by other propaganda inspired by a love of animals but conducted in an over-emotional way which is repugnant to the scientific mind.

There is, however, one animal-welfare society which provides a channel through which medical men can safely give effect to their sympathy for animals without compromising their intellectual integrity. The policy of UFAW is determined by a board of directors who are elected by the ordinary members, and these are required to have a university or professional qualification. Although a university education is not an infallible guarantee of soundness of judgment, this arrangement has in practice proved a sufficient safeguard against the influence of extremists. Moreover UFAW has found it necessary to rely largely on veterinarians and zoologists for practical guidance, thus ensuring a sound factual basis for its policies.

Its president is Dr. Edward Hindle, F.R.S., sometime regius professor of zoology at Glasgow; its scientific advisory committee is composed largely of research scientists, under the chairmanship of Prof. P. B. Medawar, F.R.S.; the president of its veterinary section is Prof. W. I. B. Beveridge, of the Cambridge Veterinary School; its technical secretary is a medical woman, Miss Jean Vinter, M.D.; and its founder and secretary-general, Major C. W. Hume, is a physicist with an amateur interest in biology.

LABORATORY ANIMALS

Most of the other animal-welfare societies in the British Isles are committed to an antivivisectionist policy, though two or three leave the subject entirely alone. UFAW is the only one which has developed a positive and constructive policy in this connection.

The UFAW Handbook on the Care and Management of Laboratory Animals, now recognised as the standard textbook on its subject, was first published in 1947, and, in conjunction with the Laboratory Animals Bureau (now Centre) of the Medical Research Council and the Animal Technicians Association, has been responsible during the past decade for a vast improvement in the comfort as well as the usefulness of laboratory animals.

The editor of the first edition was A. N. Worden, some time Milford professor of animal health at Aberystwyth and, in his student days, chairman of the students' committee of UFAW. The second edition, edited jointly by A. N. Worden and Dr. W. Lane-Petter and recently published, had to be so much enlarged that the original publishers were unwilling to publish it, although, at the same time, they were unwilling to relinquish the copyright. UFAW therefore had to buy the latter for a sum which will entail a financial loss on the whole transaction, but the object has been to provide information rather than to make a commercial profit.

More recently UFAW has turned its attention to laboratory techniques, on which it maintains a research team. A symposium last year on Humane Technique in the Laboratory was attended by about 120 research scientists. A brief report was published in this journal [1] and most of the papers have been published by the Laboratory Animals Centre as vol. 6 of its *Collected Papers*. UFAW hopes, in the first place, to see an acceleration of the replacement of animals by unconscious material in tests such as the determination of an L.D.50 or an E.D.50, which at present entail discomfort. For instance, UFAW is sponsoring a research which is being directed by Dr. Michael Chance in the medical school at Birmingham and which might, if successful, enable a wide range of such tests to be replaced by one using mice which are anæsthetised and are killed before they recover consciousness. A second hope is a reduction in the number of animals needed for a given degree of precision,[2] effected either by statistical techniques, or by genetical homogeneity of response to experimental treatments, or by detection of specific factors which effect variance. On the last point, UFAW is sponsoring a research directed again by Dr. Chance in Birmingham. (The last-mentioned research, incidentally, inaugurates a long-overdue study of the psychology of laboratory animals.) A third hope relates to refinement of laboratory techniques for the purpose of reducing or eliminating discomfort. As a contribution to this aim a UFAW research fellow, Dr. Phyllis Croft, is carrying out electroencephalographic studies of anæsthetics and relaxants in Professor Amoroso's laboratory at the Royal Veterinary College. A comprehensive review of the whole problem has been written by Dr. W. M. S. Russell, a UFAW Research Fellow, and will be published shortly by Messrs. Methuen with the title *The Principles of Humane Laboratory Technique*.

WILD AND DOMESTIC ANIMALS

But the laboratory animals are only one, and a comparatively recent one, of UFAW's interests.

1. *Lancet*, 1957, i, 1035.
2. Hume, C. W. *ibid.* 1957, ii, 1049.

The gin trap was scathingly condemned for its cruelty by several of those who spoke in defence of research when the Cruelty to Animals Act, 1876, which regulates vivisection, was passed through Parliament in 1876; yet it was finally outlawed no longer ago than July of the present year, as a result of a long campaign. An important factor in this success was a four-years' research on the ecology of the wild rabbit which was sponsored by UFAW and for which two M.SC. degrees were awarded.

Again, during a great many years some scores of thousands of unwanted dogs were killed annually by animal-welfare societies by passing electric current between the neck and the hindquarters, and strong opposition was offered, on anti-vivisectionist grounds, to UFAW's demand for a scientific investigation of the process. Eventually it became possible for Dr. Phyllis Croft, a UFAW research fellow, to make this investigation, whereupon the British Veterinary Association instituted an independent research which confirmed her finding that, in spite of superficial appearances, excruciating pain was being caused to each animal for about 12 seconds, and that this could be avoided by passing a sufficient current through the brain. For this work Dr. Croft was awarded the Livesey medal of the Royal College of Veterinary Surgeons.

Another research sponsored by UFAW is one relating to humane poisons for wild rats and directed by A. N. Worden at the Nutritional Research Centre, Huntingdon.

Again, at the suggestion of a member of the Home Office Committee on Cruelty to Wild Animals, UFAW called together and administered a committee representing zoologists, sportsmen, and others interested in the otter. A research on the ecology of this animal was undertaken with funds contributed mainly by the Nature Conservancy and to a much smaller extent by UFAW, and it is interesting to know that, although this had to be discontinued for lack of funds after two years, within a fortnight of receiving the published report the Prime Minister of Denmark made an order protecting the otter in that country.

Some time ago Prof. W. I. B. Beveridge called UFAW's attention to the painful disease of foot-rot in sheep, which is very widespread but can be eradicated if certain fully practicable steps are taken. With the support of the British Veterinary Association, the British Wool Marketing Board, the National Sheep Breeders' Association, and the National Farmers' Union, UFAW has been conducting an educational campaign on the subject, and is now sponsoring the production of a film which shows technical details of the requisite treatment.

THE NEED FOR SUPPORT

UFAW draws its funds partly from the sale of publications (and especially of Christmas cards designed by its honorary artist and chairman, Fougasse) but mainly from voluntary subscriptions and legacies. In the latter respect it is at a disadvantage in being precluded from making appeals of the sensational type, which alone open the more lavish purses. If it were to become an anti-vivisection society its financial worries would disappear overnight, but on the other hand its ability to perform its special function would be destroyed. It has therefore to rely on subscribers who are both generous and intelligent, and these are not so numerous and wealthy as could be wished.

UFAW's primary function is to create or obtain authentic information bearing upon the welfare of animals and to convey this to those who can use it to advantage, including the general public in the case of the less specialised information. To this end it is necessary to recruit support among university students, who are the professional men and women of the future, and at present there are branches in ten British universities. It is disappointing, however, that there is no organised branch in any of the

medical schools, and that the number of qualified medical supporters, though by no means negligible, is small in proportion to the size of the profession.

Information relating to the work of UFAW, including a list of publications, may be obtained from the Federation at 7A, Lamb's Conduit Passage, Red Lion Square, London, W.C.1.

The Wider World

GALEN IN CHINA

DONALD GOULD
B.Sc. Lond., M.R.C.S., D.T.M. & H.
PROFESSOR OF PHYSIOLOGY IN THE UNIVERSITY OF MALAYA

IN December, 1955, I visited China and saw something of the costly, strong, official drive to boost traditional remedies and practice. Nothing in the medical scene impressed me more, and like Fox [1] I came away feeling that political rather than scientific motives lie behind it. Under Communism, of course, all activities are supposed to contribute to the construction of the socialist State, and to this extent every movement in a Communist country is bound to demonstrate, or at least pretend, a political element. Yet it is none the less disturbing to find a naturally non-political field like that of therapeutics the subject of a determined political assault. Men trained in Western medicine are being forced to accept and adopt ancient magics.

One medical official I met early in my trip said that traditional practitioners were being given elementary instruction in health rules, and were being taught to undertake certain tasks such as vaccinations and simple treatments. He pointed out that there is still a grave shortage of Western-trained doctors; that the traditional practitioner is the village doctor of China, the man the people know and trust; and that therefore traditional doctors are being employed for certain urgent and widescale medical activities. I was left with the impression that these men are being put to good use until they can be replaced by the products of the medical schools. Since China has some 600 million people, about half-a-million traditional practitioners, and only some 70,000 doctors trained in Western methods, this seemed a wise course.

But I found later that the accent was not upon using the traditional doctor as a medical auxiliary; not upon encouraging the old to accept the new; but upon forcing acceptance, approval, and admiration of the whole established rigmarole of native therapy. In an article entitled "Why Our Western-Trained Doctors Should Learn Traditional Chinese Medicine", Dr. Fu Lien-Chang [2] president of the Chinese Medical Association, wrote:

> "How many western-trained doctors since Liberation have studied Chinese medicine and have obtained successful results? Very few indeed! The great majority of western-trained doctors have never considered the learning of traditional medicine as a task that should be undertaken seriously. The responsibility for this state of affairs lies with the health administration and the Chinese Medical Association for not having carried out their task of leadership.
>
> "Take myself for example. Although I have attended patients with practitioners of our native medicine, I have never considered Chinese medicine as a subject I should learn. I have never seriously studied any books on traditional medicine. Hence, even today, I remain a complete ignoramus as far as our native medicine is concerned. As a leader in our country's health work and as Head of the Chinese Medical Association, I am ashamed to confess this. I must seriously take up the study of Chinese medicine."

1. Fox, T. F. *Lancet*, 1957, ii, 935.
2. Fu Lien-Chang, *Chin. med. J.* 1955, **73**, 363. This article also appeared at the front of eight other professional journals.

And later:

> "In the past we have organised training courses for old-time physicians to learn western medicine. This, although necessary, is not of the greatest importance. The Central Committee of the Party and Chairman Mao have enjoined us that the key to the problem is that our western-trained doctors should study traditional Chinese medicine . . . It must be emphatically stated that not only should doctors of traditional medicine learn western medicine but, particularly, western-trained doctors should study Chinese medicine".

Dr. Fu leaves no doubt about the direction of the effort demanded. Nor is doubt left after visits, in Peking, to the Institute for Research into Herbal Medicine and the Institute for Research into Acupuncture.

THE INSTITUTES

These institutes are ill named. They are not research laboratories, but propaganda bureaus.

Acupuncture

The Acupuncture Institute, housed in a former Buddhist monastery, devotes the better part of its space to an exhibition.

The public come daily in organised groups. The tour, conducted by a hard-talking guide, takes nearly an hour. A brief account of three of the exhibits will show the tone of the place:

> A placard states that "This summer one acupuncture doctor cured 250 patients at a total cost of $12.50. By orthodox treatment, 35 similar patients would cost $339.50 to cure. On an average, each case took 1.12 days. By Western methods, each would have taken 3.5 days".
>
> A map of the world has a gleaming acupuncture needle overlying China. From this needle radiate ribands to all the other countries which have accepted and adopted acupuncture—among which England, Canada, and the United States are included.
>
> A show case holds envelopes addressed to the institute and bearing a variety of foreign stamps. They are evidence of the unsolicited testimonials which arrive daily from all quarters of the globe.

These are fair samples from a large collection of manuscripts, photographs, impedimenta, and charts, all designed to convince the layman that acupuncture is and always has been a very good thing, and that Western medicine comes a poor second.

Graphs and histograms abound. There are X-ray photographs. Statistics are worked to two decimal figures. The grubby old magic is given a fine, new, white laboratory gown.

As well as the exhibition, the institute houses "research departments" (one department, one room) of physiology, biochemistry, metabolism, pathology, bacteriology, and statistics (I am not quite sure of this last title, but it was the best I could make of the description given to me). When I was there, "research" was not yet fully under way, but the purpose of the "research departments" was clearly that of providing "scientific proof" for acupuncture's claims.

Finally, and perhaps most importantly, the institute is a training school. Doctors already trained in Western medicine are given an intensive course so that they may go back to the medical schools as teachers.

Herbal Medicine

At the Institute for Research into Herbal Medicine, a more sober tone prevails. The native practitioner who dispenses the remedies of the Chinese pharmacopoeia is very like his Western counterpart of a hundred and fifty years ago. The pretence to equality with Western medicine is therefore more easily sustained, and there is not so much need for vigorous demonstration of superiority and "scientific worth".

The institute is run like any Western clinic. There are consulting-rooms and there are laboratories and there are lecture rooms, and the traditional doctors on the staff wear long white coats and carry stethoscopes round their necks. There is also the inevitable exhibition. But, again, the accent is not upon inquiry into those remedies which appear to have some pharmacological activity; it is not upon making a critical effort to harvest what is good and reject what is useless; it is upon presenting and sustaining and increasing the influence of the whole tradition as it is and has for ages been.

It is hard to imagine how the methods of science could usefully be applied to acupuncture, but in the field of herbal medicine there is obvious ground for fruitful research. Chen and Schmidt's work on ephedrine is the classical example of what may be achieved. It is therefore disappointing to find that such work is not a major effort within the central temple of herbal medicine, and to be told, in answer to a question, that " Chemical analysis is also undertaken, but is not the main aim of research, because from some of the herbs it is not possible to extract the active principle ". The belief is encouraged that the art is being boosted for purposes other than its possible contribution to a system of rational therapy.

True enough, work of the Chen-Schmidt type is going on in China; but such efforts are largely made not at the centres of herbal medicine but in the medical schools and hospitals where Western doctors are being so vigorously urged to " cooperate " and show a lively interest in their traditional heritage.

THE FUTURE

My host at the Institute of Herbal Medicine told me of future plans.

Doctors will get their training in Chinese medicine whilst undergraduates in the medical schools. No new purely traditional doctors will be produced. The modern and the traditional modes will be taught side by side, so that after a period there will no longer be two groups of doctors in China, but a single group composed of men trained in the new synthetic lore. There will not be texts on traditional medicine and other texts on Western medicine, but new books will be written to combine the teachings of the two disciplines. There will not be teachers of the old and others to teach the new; instead each teacher will preach the double gospel, not as separate subjects, but as one. This is for herbal medicine. Acupuncture, which is a " specialty ", will have its own share of the curriculum, amounting to some 160 hours.

However, the full synthetic course will not operate until after the end of the third Five Year Plan, and that time lies ten years from now.

A more recent assessment of the situation was given last year by Ho Piao[3], vice-minister at the Ministry of Health. Reviewing the development of hygiene and health work under the first Five Year Plan, he wrote:

> " During the past few years great efforts have been made in developing traditional medicine. In China there are now more than 500,000 traditional practitioners with over 40,000 apprentices. Four colleges for the teaching of traditional Chinese medicine have been opened together with six schools and twenty-three centres for refresher courses. In addition there are 144 hospitals and 453 clinics where traditional Chinese medicine is practised exclusively. Over 20,000 traditional doctors have joined the government health service. At present 5,000 highly trained modern doctors are studying traditional medicine, among whom 300 are devoting their full time to it. An institute for research into traditional medicine has been established. All colleges of medicine and pharmacy pay particular attention to research into traditional Chinese medicine and pharmacy ".

This statement hardly suggests that the pure herbalist is on the way out; on the contrary it shows that earlier plans for boosting traditional medicine are being vigorously pursued. So far as " cooperation " between the old and the new is concerned, the picture seems wholly one-sided. " 5,000 modern doctors are studying traditional medicine " (despite the crying need for their efforts in other tasks). There is no mention of traditional doctors being trained in Western ideas.

A marriage having been ordained, one unwilling partner is being steadily forced by determined in-laws toward an unhappy consummation. How will the children turn out?

3. Ho Piao. *ibid.* 75, 953.

INCOMPATIBLES

There is no strict proof that the ultimate will of God is expressed in the being of the Royal College of Physicians of London (however some of the Fellows may feel); and, on the other side, there is no doubt that the herbal doctor in China provides, and has for centuries provided, services sorely needed by a sick man and his relatives. The choice between modern and traditional medicine is not, therefore, a choice between the ideally good and the wholly bad. Nevertheless an equally absolute difference does divide the two. One is science and the other is not.

Herbal medicine is a mixture of empiricism and superstition: acupuncture is unspoiled magic. The whole nature of contemporary Western medical thought and practice rests upon the rules of science. It is therefore logically impossible to teach the two systems effectively side by side; for a man who believes in the one cannot appreciate the other. It must follow that a man cannot teach or learn or practise both together unless he avoids thinking about either.

The whole medical effort must be reduced to the faithful practice of decrees. Doctors must recognise the Party as the only competent authority in medicine, as in all else. And first among the results to be expected is that advance will cease. Medicine in China must look forward to a period of inanition exactly parallel to that which seized medicine in Europe for centuries under the grip of the galenical philosophy. The only advances permitted will be those introduced from outside after careful vetting and approval by the State.

Is this what is required and foreseen?

AN EXPLANATION

I have two reasons for suggesting that the Chinese Government does want and expect the results I have imagined. Firstly it is an accepted working rule of historians that an intelligent man foresees the logical consequences of his deeds; and there is certainly no doubt that the present leaders of China are highly intelligent. Secondly, it is significant that the full synthetic training is not to be introduced for another ten years. Mao Tse-Tung pronounced the need for cooperation between modern and traditional doctors in October, 1944. Admittedly, the training of teachers and the writing of texts must precede remodelling of the medical course, but by Communist standards, twenty-four years is a strangely long preparatory period, and out of keeping with what we know of their usual rate of progress towards a decided end. However, if the leaders realise how their programme must alter the whole nature of medical thought and practice in China, then another reason for delay emerges:

> The present structure of medical services and medical training must depend largely upon the work and enthusiasm of doctors and medical scientists who have had their training in Western schools, either inside or outside China; many of the best of whom will have spent some time abroad in postgraduate training and practice. It is essential to retain the effective services of these men until they can be replaced by more amenable domestic products. It would be impossible to bring about their genuine conversion to the ancient faiths. The Government is showing its wisdom in not risking shipwreck by forcing too sharp a change of course.

Then, if the consequences are foreseen, what is the motive? It is certainly nothing trivial like a misguided chauvinism, or an undue influence by vested interests in high places. The effort is far too large, the results too

grave, to allow belief in such answers. Is the movement inspired by a deep governmental faith in the "scientific" virtues of traditional medicine? That would be a curious judgment from a group of hardheaded dialectical materialists. Is it simply an attempt to make the native cures seem good to the people in view of the fact that for many years to come no other sort of medical care will be available to most of China's millions? This would be a satisfying answer if the main effort was in public propaganda supporting herbalism. It is no explanation for the changes being forced upon Western practice.

Possibly there is no one answer, and possibly some or all of the factors just considered helped to shape policy; but I suggest that a prime and purely political motive lies behind all:

The doctor, unlike the chemist or the physicist or the engineer, is necessarily always in close contact with the people of the community he serves; and if he is any good at all he has a large, personal, and direct influence on his patients and on his patients' friends and relations. I suggest that a man trained in the critical and almost iconoclastic school of contemporary Western medicine is not a suitable person to wield moral and intellectual authority among the citizens of a Communist State. If he himself is a dedicated believer in Marx-Leninism, he may achieve a sort of working schizophrenia, having a mystical faith in the gods of State, whilst keeping a fairly effective spirit of independence and inquiry alive within the half of his mind that he uses for his job. When conflict occurs, as sometimes it will, the mystical half of the mind will prevail, and the professional half will suffer a few blind spots —but probably not too many or too large to cripple him as a scientific doctor.

However, most citizens in a Communist State are not dedicated Communists (any more than most citizens in a democracy are dedicated Democrats or Conservatives), and it is the educated but undedicated who is most likely to become the revisionist, the dangerous liberal, the traitorous reactionary.

I suggest that the Government of the People's Republic of China realises full well that it cannot risk educating tens of thousands of young men and women into the habits of critical thought regarding people, and self-reliance in handling people, that a man must have for the successful practice and understanding of modern Western medicine. Even less can the State afford to let such hordes of dangerous thinkers loose among the masses. I believe that the forcible dilution of Western medicine with old magic is an attempt to produce a new species of medical animal, still capable of acting in a priestly role as comforter of the sick, still capable of practising modern and indispensable techniques according to the book, but without that perilous turn of mind that kicks against the pricks and asks a sound argument for every thesis.

APOLOGIA

To Western and non-Communist minds this explanation may appear impossibly far-fetched. The danger to the State that I have conjured up is so nebulous; the remedy so heroic. But the curious happenings are there and must be explained. Consideration of two relevant circumstances may make my interpretation seem less fanciful:

To a true Communist there is only one, supreme, inviolable science, and that is the science of Communism. All other facts, disciplines, and behaviours must fit the sacred doctrine, or change to fit, or be abolished. What to an unpolitical scientist seems grossest cynicism or illogic, may to a Communist appear as common sense. In the Communist vocabulary, expediency is a synonym of truth. I stress this not as political criticism (which is not the purpose of my writing) but to make the point that the assault on medical science taking place in China today is not necessarily inspired by motives that would make good sense to a non-Communist mind. Indeed, to the Communist mind, the happenings here described may not appear as an assault at all.

The second circumstance is peculiar to China. Before the Communist revolution the better medical schools were largely run by foreigners. The outstandingly excellent Peking Union Medical College was owned by the China Medical Board, endowed from Rockefeller funds. Many of the others of good standing were owned by missionary societies.

For years the Chinese had resented foreign management of their affairs, and I have the impression that missionaries were resented more than most, despite their simple wish to serve. Because of this foreign hold on medical education and services, the profession in China had closer links with the unpopular West than any other important native group. When the Communists drove south and took the land, they must have looked with particular suspicion upon the doctors who had been nurtured by American gold and Caucasian Christians.

One last implication. The new Chinese medicine can flourish only if its practitioners are kept effectively isolated from Western thought. It is difficult to see how isolation can be long maintained whilst both outlooks survive. Possibly the active promotion of the one betrays an assumption that the other faces short shrift.

Public Health

ANTIVACCINIAL GAMMA-GLOBULIN IN SMALLPOX PROPHYLAXIS

E. R. PEIRCE
M.R.C.S., D.P.H., D.T.M.
LATELY MEDICAL OFFICER IN CHARGE OF NEW FERRY ISOLATION HOSPITAL

F. S. MELVILLE
M.B. Edin., D.P.H.
MEDICAL OFFICER OF HEALTH, BEBINGTON

A. W. DOWNIE
M.D. Aberd., F.R.S.
PROFESSOR OF BACTERIOLOGY IN THE UNIVERSITY OF LIVERPOOL

MARJORIE J. DUCKWORTH
M.B. Lpool
ASSISTANT LECTURER IN BACTERIOLOGY IN THE UNIVERSITY

GAMMA-GLOBULIN prepared from adult serum has been used successfully in measles prophylaxis for some years, and since 1956 gamma-globulin, prepared from the serum of recently vaccinated or revaccinated adults, has been available, through the Public Health Laboratory Service, for smallpox contacts. As yet, however, there is little evidence as to the efficacy of this antivaccinial immune globulin.

Field trials were reported by Kempe, Berge, and England in 1956. In Madras, in 1953, 56 household contacts of smallpox cases were vaccinated and given vaccinia immune gamma-globulin, while a control group of 75 household contacts were vaccinated only. Of the first group 2 subsequently developed smallpox and 1 died, while in the control group there were 8 cases of smallpox with 3 deaths. In the same report evidence is presented of the value of gamma-globulin in the prevention of generalised vaccinial infection in eczematous children who required vaccination or who were exposed to recently vaccinated children.

In the Tottenham outbreak of smallpox last year vaccination was supplemented by vaccinia immune gamma-globulin for primary contacts who had not been previously vaccinated

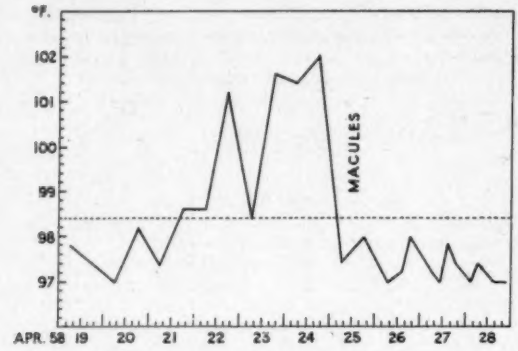


Fig. 1—Temperature chart of case 3, J. L., aged 6.

(Hogben, McKendrick, and Nicol 1958). None of these developed smallpox.

The recent occurrence of smallpox on Merseyside provided an opportunity to observe the effect of gamma-globulin, prepared from the serum of recently vaccinated individuals, on close family contacts of the second case.

History of the Outbreak

THE FIRST CASE

The *Circassia* arrived at Liverpool on the evening of March 19, having on board a coloured seaman with smallpox. He had become ill on March 9, eleven days after leaving Bombay, and the rash had appeared on March 12. On arrival he had a severe confluent pustular eruption. He was landed by the fireboat *William Gregson* and taken by ambulance to the Smallpox Hospital, New Ferry. By March 24 the lesions were drying up.

At the Smallpox Hospital the usual precautions were taken about disposal of scabs, disinfection of floors and disposal of bed linen. After the patient's admission no-one entered or left the hospital grounds except medical personnel and the matron of the parent hospital. Stores were sent from the parent hospital; milk and groceries were left outside the main gates.

THE SECOND CASE

Family L. lived in a row of houses about 400 yards from the Smallpox Hospital.

The son, T. L., aged 1 year and 11 months, unvaccinated, had been confined to his home for a fortnight before March 21, because of mumps. On March 25 he was taken by his mother to the hairdresser's. On April 6 he appeared to be suffering from a heavy cold and was generally " out of sorts ". On April 9 a rash appeared on his face, and next day it had spread to his arms and legs. On April 14, at his doctor's request, he was seen by two of us (F. S. M. and E. R. P.); a diagnosis of severe discrete smallpox was made and he was admitted to the Smallpox Hospital. The eruption was pustular, semiconfluent on the face, and profuse on the extremities. He was extremely ill. From admission he was given one million units of penicillin daily. On April 18 his condition was still very poor, and 2·5 mg. of cortisone in orange juice was given twice daily by mouth for three days. On April 20, when the lesions were beginning to dry up, he showed definite improvement, and with the fall in temperature next day cortisone and penicillin were stopped. By May 8 most of the crusts had separated, though a few remained on the scalp. He was discharged from hospital on May 17.

T. L. had been at home during the first six days of the eruptive stage of his illness and his family contacts had been heavily exposed. They were his father, Mr. L., aged 37, vaccinated in infancy and during war service; his mother, Mrs. L., 40, vaccinated in infancy and again successfully in 1946; his sister, J. L., 6, unvaccinated; and his grandmother, Mrs. K., 73, vaccinated in infancy. These family contacts were vaccinated on April 14 and kept in isolation at home. (Other known contacts of T. L. were vaccinated between April 14 and 16.) But J. L. and Mrs. K. had been heavily exposed to infection for so long that vaccination seemed unlikely to protect them. Immune gamma-globulin was sent by Dr. J. C. McDonald of the Central Public Health Laboratory, Colindale, London, and on April 15 1·5 g. dissolved in 12·5 ml. distilled water was injected intramuscularly into J. L., and 1·0 g. similarly given to Mrs. K. On April 16 a further 0·5 g. was given to J. L.

Reactions to vaccination.—Mr. and Mrs. L. both had accelerated reactions maximal about the fourth day. Mrs. K. had the reaction characteristic of primary vaccination, with axillary adenitis, and after nine days the large vesicular take still showed no sign of drying. The reaction of J. L. was also primary in type but without adenitis. At eight days she had a small vesicle surrounded by a well-marked areola, but next day this was much less and a central scab had formed—rather earlier than might be expected in a typical primary take.

THE THIRD CASE

On April 21, seven days after vaccination and twelve days after the appearance of the focal eruption in her brother, J. L. had a slight evening rise of temperature.

Her temperature chart is shown in fig. 1. During these days when the temperature was raised she had no headache, backache, or sore throat; she felt quite well and played at home during the day. On April 25, when her temperature had returned to normal, two small red papules were present on her right forearm, one on her forehead, and one macular lesion on the back of her right hand and one on her left thigh. Scrapings from the lesion on the back of her hand showed no virus on direct microscopical examination but produced typical variola lesions on the chorioallantois of chick embryos. Next day a few more lesions were seen: fig. 2 shows the position of all the lesions on April 28. From lesions scraped on April 26 and 27 smallpox virus was recovered on inoculated chick embryos. The patient had been removed to the Smallpox Hospital on April 26, but she had no further rise of temperature. The lesions never developed into typical smallpox pustules; some developed tiny vesicles before drying up and others never progressed beyond the papular stage.

Had she not been under daily supervision this child would not have been recognised as a case of smallpox.

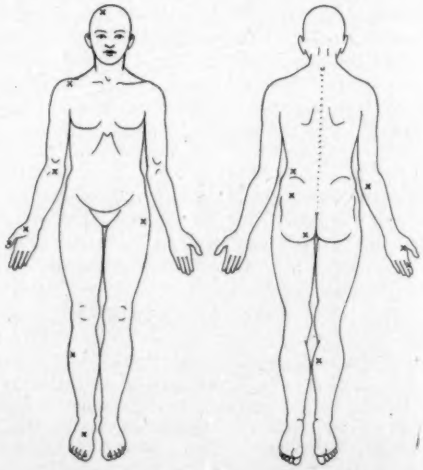


Fig. 2—Distribution of eruption in case 3.

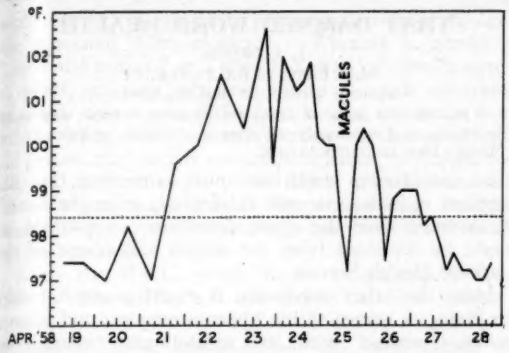


Fig. 3—Temperature chart of case 4, Mrs. K., aged 73.

THE FOURTH CASE

Mrs. K., the grandmother, also had a slight rise of temperature in the evening of April 21.

Next day her temperature was higher and she complained of axillary adenitis apparently due to her vaccination which was vesicular at this time. Her temperature chart is shown in fig. 3. On April 23 she had a profuse discrete macular rash and was admitted to the Smallpox Hospital. Next day the rash was generalised like that of a severe rubella. It was absent from the face, sparse on the hands and feet, but profuse on arms, back, chest, abdomen, and thighs, and confluent over the scapular and lower lumbar region. This was probably a prodromal rash. Scrapings taken from the eruption on the left forearm failed to show virus by inoculation of chick embryos.

On April 25 her temperature was normal and the generalised rash was fading. She had a few maculopapular lesions, however—one on each thigh, one on left forearm, and one on the right thumb. Scrapings from this last lesion showed virus particles on direct microscopical examination and produced typical variola lesions on the chick chorioallantois. On April 28 focal lesions, rather atypical in distribution, were present as shown in fig. 4. From lesions examined on the 26th and 27th virus was recovered by chick-embryo inoculation. Some of the lesions had become pustular by the 27th and 28th but they dried up thereafter.

Although this patient had rather more general disturbance than J. L. (case 3), and had an extensive prodromal rash, there was no secondary fever and the illness ran a mild course.

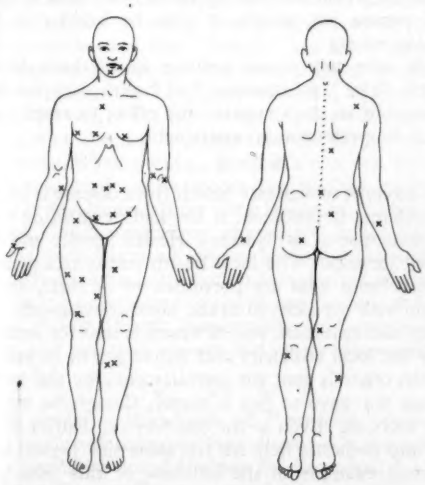


Fig. 4—Distribution of eruption in case 4.

Garglings

Garglings usually contain virus from about the time that the focal rash appears (MacCallum, McPherson, and Johnstone 1950, Downie and McCarthy 1954).

Garglings had been collected from cases 3 and 4 daily from April 18 to 29th inclusive—i.e., from three days before the onset of fever until eight days thereafter. They had been kept at −70°C until examined on May 1, 6, and 9. Specimens were spun at 10,000 r.p.m. for thirty minutes, and the deposit (suspended in fluid containing streptomycin and penicillin) was tested for virus by inoculation on the chorioallantois of chick embryos. From none of the specimens was virus recovered even by two or three passes of the inoculated membranes to further chick embryos. That virus had not disappeared from the specimens during storage was suggested by examination of garglings from case 6. A specimen taken from this patient on the seventh day of illness was heavily infected with virus, and the titre had not diminished after a month's storage of a portion of the specimen at −70°C.

Neither case 3 nor case 4 ever showed any obvious lesions in the mouth, and the failure to find virus in garglings suggests that their throat and mouth secretions were not highly infective.

THE FIFTH AND SIXTH CASES

As contacts of case 2 had been kept under surveillance until May 1 and no further case had been reported up to May 10, the outbreak was thought to be at an end. However, a man, Mr. G., aged 54 (case 6) was admitted to Clatterbridge Hospital as a case of meningitis on May 17. He had a hæmorrhagic rash and was extremely toxic. He was seen by two of us (F. S. M. and E. R. P.) several hours after admission and recognised as a case of hæmorrhagic smallpox.

He was removed to the Smallpox Hospital where he died three days later. Material from his skin lesions showed virus on laboratory examination. As his wife was known to have been a contact of case 2, this man, who had been vaccinated in infancy only, had been revaccinated on April 16. This vaccination produced no take and he was told by the health visitor, who called daily, that he should report to the clinic to have the vaccination repeated; but he did not see fit to do so. His illness began on May 12, but he went to work this day and the next. He visited his doctor on May 17 and from there was sent to hospital.

His contacts, including those at the doctor's surgery and at the general hospital, were vaccinated, and 9, who had not previously been vaccinated, were given immune gamma-globulin. None of these contacts developed smallpox.

As the wife of case 6 had visited the home of case 2 just before case 2 was admitted to hospital on April 14, she was examined immediately after the nature of her husband's illness was recognised.

On May 18 there appeared to be a few old crusting lesions. From three of these, one in the palm of the hand and two on the trunk, crusts were removed and extracted together for inoculation of chick embryos. Smallpox virus was recovered. This woman (case 5) had been vaccinated in infancy and again on April 15, one day after contact with case 2. This last vaccination gave a good slightly accelerated primary take which left two good scars. She had been visited daily by a health visitor until May 1, but no illness had been recorded. On May 1, 2, and 3 she had an influenza-like illness. This illness occurred seventeen days after her last possible contact with case 2 and eleven days before her husband sickened.

If this woman's illness on May 1–3 was mild smallpox, the incubation period was longer than that usually accepted (ten to fourteen days) and the incubation period of her husband (case 6) rather less than the average.

Discussion

This outbreak was one of variola major originating in India. The first 2 cases were extremely severe, with semiconfluent eruptions, while the 6th case died of a hæmorrhagic form of the disease. It is difficult to assess the prophylactic value of gamma-globulin given to contacts of cases, because of the uncertainty of infection being acquired by such contacts.

Only planned experiments such as that of Kempe et al. in India can quickly provide conclusive evidence. Nevertheless, the observations on cases 3 and 4 suggest that immune gamma-globulin greatly ameliorates the course of smallpox after infection has been acquired. These 2 patients, one unvaccinated and one vaccinated over seventy years previously, had been for several days in contact with case 2 before the diagnosis of smallpox was made. If one allows for an incubation period of twelve days in cases 3 and 4—although this may have been prolonged by the administration of gamma-globulin—vaccination was not carried out until the fifth day after their infection. Primary vaccination at this stage in the incubation period is believed to have little protective value. While the immunity response after revaccination may be fairly rapid (McCarthy, Downie, and Bradley 1958) the primary type of take shown by Mrs. K. indicated that she had little or no residual immunity from her childhood vaccination. We believe that the extremely mild course of infection in case 3 and the mild smallpox in case 4 can be attributed to the gamma-globulin given to these patients seven days before their illness, and not to their successful vaccination. The absence of virus from their garglings is not altogether surprising since neither patient had detectable lesions in the mouth or pharynx.

The dose of gamma-globulin given to case 3 (aged 6) was 2 grammes—twice the dose recommended for adult contacts. This represents several hundred millilitres of vaccinia convalescent serum. The gamma-globulin used was tested for variola-neutralising antibody by the chorioallantoic membrane technique (McCarthy and Downie 1953). A 1% solution gave more than 50% neutralisation of variola virus in fivefold dilution up to and including the dilution of 1 in 125.

Mrs. G. (case 5) also had a mild infection; but the mildness of her disease can probably be attributed to vaccination in infancy followed by successful revaccination the day after her contact with case 2.

Summary

The outbreak of smallpox in Merseyside comprised 6 cases, the first being an Asiatic seaman infected in Bombay.

The 2nd case was a boy about 2 years old who remained at home for the first nine days of his illness.

In close contact with him were his sister aged 6 (case 3) who had never been vaccinated and his grandmother aged 73 (case 4), vaccinated in infancy.

These were vaccinated seven days before the onset of their clinical infection, but probably this had little effect. The mildness of their illness is attributed to immune gamma-globulin given on the day after their vaccination.

REFERENCES

Downie, A. W., McCarthy, K. (1954) The Dynamics of Virus and Rickettsial Infections; p. 194. New York.
Hogben, G. H., McKendrick, G. D. W., Nicol, C. G. (1958) *Lancet*, i, 1061.
Kempe, C. H., Berge, T. O., England, B. (1956) *Pediatrics*, **18**, 177.
MacCallum, F. O., McPherson, C. A., Johnstone, D. F. (1950) *Lancet*, ii, 514.
McCarthy, K., Downie, A. W. (1953) *ibid.* i, 257.
— — Bradley, W. H. (1958) *J. Hyg., Camb.* (in the press).

THAT DAMNED WORD HEALTH

I. GORDON
M.D. Edin., M.R.C.P., D.P.H.
MEDICAL OFFICER OF HEALTH, ILFORD

"Health is a state of complete physical, mental, and social wellbeing, and not merely the absence of disease or infirmity."—WORLD HEALTH ORGANISATION.

IN considering health we must remember that the problem is biological—not theological, as might almost be assumed from the above definition,[1] or political, as might be supposed from the origins and course of the National Health Service.

Man, like other organisms, is evolving continuously, for better or worse, within his environment; and when a person's contact with his environment, internal or external, is deleterious, he is bound to suffer some damage, though this may not be permanent or even appreciable. He makes an effort to overcome any disability thus caused; and numberless times during his lifetime each individual moves from apparent defeat to apparent victory. An apparent defeat may cause the effort leading to apparent victory, and an apparent victory the lack of effort leading to apparent or real defeat. For defeat read illness; for victory, health.

To maintain his equilibrium with his environment, man and his species are in perpetual struggle—with microbes, with incompatible mothers-in-law, with drunken car-drivers, and with cosmic rays from Outer Space. How then, in this context of movement and buffeting back and forth between organism and environment, can we find any place for the woolly-headed definitions of "positive health", as a state that can and must be considered apart from disease? It is as if we were to insist on discussing white without mentioning black; hot, without intruding with that dreadful word cold. In the living there is no such thing as complete health, any more than there is complete disease (which is death): each organism is somewhere between the two, as each temperature is somewhere between absolute minimum and absolute maximum. We all of us have something of disease with us, even if it is only an acne spot today and food-poisoning tomorrow. Disease began to corrode us the moment we were conceived, if not before. In fact, we may be higher up the ladder of health by virtue of some imperfection; as the life-history of many a handicapped person has shown, it may be healthy to have something wrong.

People who talk about positive health have become confused. The "positiveness" of health does not lie in the state, but in the struggle—the effort to reach a goal which in its perfection is unattainable.

* * *

This attempt to separate health from disease is of more than academic importance: it has had devastating effects on the structure of the National Health Service and other statutory services. The local health authorities generally deal with those who are presumed to be well, and the hospitals with the sick; so in the same convalescent home one may find two men, one of whom is sent for recuperation by the local authority and has to pay or be assessed, while the other is sent for convalescence by the hospital and does not have to pay a penny, though he may not be any more ill. Even in the one service, district nursing is free and domestic help for the same sick person is not. The worst example of the outcome of this false philo-

1. See also "A Study in the Epidemiology of Health", published by the Kent Pædiatric Society from 14, Brampton Road, Bexleyheath, Kent.

sophy is that local-authority welfare activities for the aged are separated from medicine. Whether a person is "aged and infirm" or "aged and sick" is often a matter of doubt, and may vary from day to day; it is something on which doctor may differ from doctor, or doctor from welfare officer. Yet on the opinion which prevails the old person may receive accommodation or be denied it—may be made to pay or freed from monetary worries. Even the expectant mother bears a smaller financial burden if she enters a maternity hospital than if she is confined at home.

When the B.B.C. produced its programme "Your Life in Their Hands," the *British Medical Journal*[2] accused it of concentrating on "disease education". It suggested that disease should not be discussed on television, where the emphasis should be on health. But of course it is quite impossible to discuss health with intelligent people without simultaneously discussing disease. Are we to tell the inquiring student of health not to smoke without describing bronchitis or cancer of the lung, or what to eat without telling him about scurvy, rickets, or beriberi? The *British Medical Journal* points out that the operative word in the National Health Service is *Health*, as if this somehow disguises the fact that fundamentally it is a bed-and-bottle service. Even the World Health Organisation, in spite of its name and its erroneous definition of health, concerns itself (and quite rightly) mainly with disease, as does the Ministry of Health.

Medical officers of health themselves are not always clear about the impossibility of separating health from disease. They, and the Ministry of Education, tend to evaluate school medical inspections by the number and accuracy of the defects noted: if none are noted, either the examining doctor didn't do his job properly or the child was perfect. It is not so; all children have defects, and the fundamental job of the school medical officer at a routine examination is to decide which are significant and to inform the parents accordingly. The lists of defects that obsess clerical staffs and the Ministry are but a minor, inaccurate, and variable excretion of a very important (even though hurried and harassed) medical examination. Inasmuch as this evaluation of the indefinite borderline between health and disease concerns every child, such work is even more important than the highly specialised technique of advising the obviously handicapped.

My colleagues in public health have tended to adopt the fashionable view that "health" is a more noble term than "medicine" because the latter implies contact with disease. Hence the imaginary elevation of the School Medical Service to the School Health Service. However, they are now coming to regret this, for Health does not pay as well as Medicine (i.e., disease), nor are its exponents as well respected. The sooner the Society of Medical Officers of Health insists on using the terms "community medicine" or "community physician" in its title, and drops the word "health", the earlier will it command the attention it deserves in the nation's counsels. Let the word health be the prerogative of the Royal Society of Health and the Public Health Inspectorate, and others whose training and function are not intimately connected with disease.

* * *

When there is discussion of "positive health"—a state to be considered apart from disease—in the words of the late but unlamented German field marshal, "I reach for my gun".

2. *Brit. med. J.* 1958, i, 510.

In England Now

A Running Commentary by Peripatetic Correspondents

Charles was always a bit of a devil for making a clean sweep. Perhaps some radical streak in his nature led him to take up surgery. Perhaps the disciples of that art are inclined to favour total extirpation of any pretty frills that stand in the way of stark function. It all seemed rather heroic from my end of the table. I used to give dopes for Charles in the old rag-and-bottle days, and I remember watching him open up an abdomen that had defied the diagnostic skill of physician and surgeon alike. In went his hand for the lucky dip, out popped a rather seedy looking appendix. Charles eyed it with distaste. Its obvious chronicity offended his dignity: by all rights it should have burst during the attack before last, but it did not: it lay there across his finger and sneered back. Charles performed his usual pretty appendicectomy as a sideline to a dissertation on downdraught carburettors, and pushed the rest back. He rummaged about in the pelvis and his eyes lit up. With some difficulty a fibroid uterus was coaxed out under the floodlights, and we were treated to a gynæcological exhibition turn for the next twenty minutes. After the hysterectomy I was getting ready to doze off myself with the warmth and the ether fumes, when Charles complained profanely that the patient was not relaxed enough for him to get on with the original aim of an exploratory laparotomy. I sighed and Mrs. Ugglethorpe sank deeper into oblivion. Her gallbladder was rattling like a dice-box with stones, so she lost that little lot. There was rather a hollow echo as her abdominal wall was stitched. She could never complain that she had not had her money's worth. Actually she did very well afterwards, but that is beside the point.

Charles lives about thirty miles outside Town, and has the sort of garden that consultants are expected to have. He also has no gardener. Twin carburettors and an elegant suite of rooms in Wimpole Street are completely neutralised if appearances are not kept up at Riverside Lodge. The grass was too long and tough for a mower. Charles did not think that his lumbar discs would endure sufficient torsion for the good old-fashioned scythe. Mary refused downright to get on her knees with the shears, and managed to persuade him to hire the mechanical scythe from the golf club. On Sunday afternoon he started it up and trundled the thing chattering towards the lawn. It made a grand job right across the mid-line. We waited for Charles to swing it round the other way: he was red in the face and running by then: the engine was roaring, so was Charles. Straight over the rose beds they went. Fanny Blankers-Koen was overtaken, Mrs. Sam McGredy was cut off in her prime, General MacArthur fell to the sword, Anne-Else and Karen Poulsen were guillotined in one unhappy family group. On through the borders in front of the house. Azaleas, red hot pokers, carnations, and delphiniums fell in piles. So did *Hamamelis mollis*. I had visions of Mary being trapped against the wall and serially sectioned by the runaway microtome, but, with a last despairing wail, Charles tugged at the offside handlebar and then let go. The aid to surgery fell into the river.

I was most unpopular for mentioning Mrs. Ugglethorpe.

* * *

Malaria is not a disease which one expects to see every day, or indeed every other day, north of Hadrian's Wall. I was slightly taken aback, therefore, to be summoned by my Chief to see a case of malaria late one evening.

By the time I arrived he had departed and I was left with the problem. But the blood-film confirmed the diagnosis, and only the knowledge that the Chief had been a classical scholar in his youth prevented me from sending him a telegram: Veni, Vidi, Vivax!

* * *

Mrs. McLaren, despite her name, was French. She was in her 76th year, immensely entertaining, and remarkably vivacious for a woman of her age. Unfortunately her gallbladder was full of stones and she had been admitted because of

recurring attacks of severe biliary colic. Operation was advised and was firmly refused for no very definite reason. I resolved to make a final persuasive effort but she shook her head and said, " I am very stubborn; my mother used to say I was the most stubborn woman in Paris."

Then I remembered the charming Oscar Wilde story of the lady who prided herself on her lack of beauty. Bravely embarking on my patient's native tongue I began the tale: " Dites-moi, Monsieur, si je ne suis pas la femme la plus laide à Paris?" " Mais, Madame, dans tout le monde!" Wilde, the kindest of men, recorded that the lady was delighted. So was Mrs. McLaren. Almost embracing me, she cried, " Très bien, Monsieur le Docteur, très bien. My gallbladder, it is yours."

* * *

For the annual general meeting our society usually manages to muster some 5% of its membership, consisting of the executive committee plus a few rash youths who lack enough intelligence to understand that regular attendance at annual meetings (i.e., attendance at two consecutive meetings) carries a grave risk of nomination and unanimous election to the executive. Myself, I was very shabbily treated. As a newcomer I attended two A.G.M.'s, but when I skipped the third I was nominated and elected to the executive *in absentia*. The first I heard of this was 10 months later, when I was summoned to the next meeting of the executive. Sense of responsibility made me attend subsequent meetings, until after about 7 years I realised that all of the older members had " been through the chair ". While I was vice-chairman, I was reprieved when it was suggested that the chairman should hold office for a further year. This had happened only once before; but I was prepared to ignore the apparent insult, in return for not having to officiate at our first annual dance.

You see, I last went to a dance shortly before the war. In those days I was courting hard, and affected a personal version of the soft-shoe-shuffle. But 19 years is a long time; something had to be done despite the year of grace. After 11 months of procrastination, and an urgent phone call to a local dancing academy, I attended a " private lesson " session. Everyone was very kind to me. One lesson taught me the rudiments of a slow waltz, and one the basis of a quickstep. Each night I lay awake, twitching; one, two, together: or slow, slow, quick-quick slow.

When the great day came, of course there were so many people there that, whatever their abilities, there was no room to do more than the old soft-shoe-shuffle. (What is the use of learning to dance if on the floor one cannot go ahead on a north-north-westerly bearing for another two yards, without hazarding the ship and sinking with all hands on each leg of the course?) By 11 P.M. I was ready for bed: by 1 A.M. I was out on my feet, the only sign or symptom of continuing consciousness being a splitting headache. At 2 A.M. I was allowed out to relieve the baby-sitter. My halo lay heavily on me when I found that everybody seemed to think that I had enjoyed the proceedings as much as they had.

I really must get on with these dancing lessons in good time this year. The duties of chairman at such a function are hardly onerous enough to excuse him from taking the floor at all.

* * *

Perhaps it was subconscious confusion which led a pupil midwife in answering a question about the virtues of breast-feeding to write, " The breast-fed baby is more contented as it lies curdled in its mother's arms."

* * *

Junior Partner: I thought you said you believe in telling the patient the truth.

Senior Partner: So I do.

J.P.: Then why did you tell Mrs. P . . . that she had a strong heart? In fact you said she has an " exceptionally strong heart ".

S.P.: So she has.

J.P.: How can she, when she's had coronary thrombosis twice and has a blood-pressure at least double your own?

S.P.: My boy, any heart which can support a blood-pressure of those dimensions after two thromboses must be exceptionally strong!

Letters to the Editor

UBIQUITOUS STAPHYLOCOCCUS

SIR,—We are all, now, familiar with the ubiquity of the staphylococcus in the hospital air and dust and with its deadly characters. So much has in fact been written and so intense has been the attack on typing and categorising the organism that we are rapidly losing sight of the most urgent need—a return to the practice of aseptic method.

I have recently made post-mortem examinations on patients who, having survived postoperative pulmonary embolism, have died with staphylococcal abscesses within the pulmonary infarcts. In some of the cases there had been a staphylococcal wound infection in the immediate postoperative period.

Bacteriological examination of necropsy material, so often neglected, continues to provide a sinister reminder of the omnipresence of the staphylococcus and points clearly to the remedy—aseptic method.

This remedy will prove expensive in staff and materials. Nevertheless it must be applied sooner or later. We are asking too much of the human body and its powers of resistance to injury when we add to deadly pulmonary embolism the mortal blow of staphylococcal toxæmia.

Department of Pathology,
University of Cambridge. G. A. GRESHAM.

IMPORTANCE OF INTRAVENOUS INJECTION OF DIPHTHERIA ANTISERUM

SIR,—I read the article by Dr. Tasman and his colleagues [1] with considerable interest. They suggest that the intravenous injection of antiserum in patients suspected of having diphtheria ought to replace the still common practice of giving it intramuscularly, for the following reasons:

(1) 100% of the highest antitoxin titre is obtained the first day after the injection.

(2) The saliva contains antitoxin after only 30 min.

(3) The advantages of intravenous injection were clearly illustrated by the protection of guineapigs injected with lethal doses of diphtheria toxin.

I think, however, that their process of reasoning is not altogether free from criticism:

(1) The intravenous injection of a certain amount of antiserum gives 100% of the highest titre (how many antitoxin units in the blood?), when given intramuscularly only 50% (table II, p. 1299). If, however, we inject intramuscularly twice as much antiserum, or more, the antitoxin titres the first day after the injection may be the same.

(2) The early or late excretion of antitoxin in the saliva is not a significant phenomenon; if antitoxin titres in the blood are adequate they neutralise the absorption of the toxin with the saliva.

(3) The experiments on guineapigs cannot be transferred to man: the moment of infection is not known, and in the experiments with guineapigs the same doses of antitoxin have been used in intramuscular and in intravenous injections. Another experiment, giving the guineapigs twice as much antitoxin intramuscularly, might be profitable.

On the question of anaphylaxis, I do not think any test gives 100% guarantee of safety. Although in my clinic we use a well-purified antiserum only intramuscularly, never omitting the skin test, and although we inject the antiserum in small doses at intervals, we have had a few rare instances of serious allergic reactions.

The amount of antiserum injected for diphtheria varies considerably in different countries and is often based on

1. *Lancet* 1958, i, 1298.

tradition, or on more or less statistically evaluated results of treatment; but we have no exact theoretical means of estimating the amount of antitoxin really needed.

Clinic for Infectious Diseases of Childhood, Warsaw. J. BOGDANOWICZ.

TREATMENT OF BREAST CANCER

SIR,—The declared object of radical mastectomy as well as of limited mastectomy plus subsequent radiotherapy is to eradicate all tumour tissue from the chest wall and from the axilla.

Success or failure may or may not be reflected in the five-year-survival rate, which is influenced by such other features as clinical stage and histological character of the tumour. The effectiveness of these treatments could, however, be expressed by stating the proportion of patients who: (*a*) remain free of any clinical manifestation of the disease on the chest wall or in the axilla for five consecutive years after the first intervention; (*b*) die within five years without such manifestation (of metastases); (*c*) survive for five years but show disease on the chest wall or in the axilla; (*d*) die within five years with, but not necessarily of, disease on the chest wall or in the axilla.

These results should be stated for each of the various stages according to a simple (Steinthal) classification. Such information from those who are in a position to analyse a large number of cases would present a more rational basis for advice on appropriate treatment than many of the statistics which have little clinical significance.

Radiotherapy Department, St. Mary's Hospital, London, W.2. M. HULBERT.

CHLORPROPAMIDE

SIR,—I am interested in the account of the trials of chlorpropamide reported by Dr. Murray and his colleagues in your issue of Sept. 13. Unfortunately my experience in treating a similar group of 43 diabetics has not been correspondingly satisfactory, nor yet as good as mine with the generally abandoned carbutamide.[1]

The investigation began in February, 1958. 43 diabetics had chlorpromazine, but only 3 were under observation as inpatients. There were 11 men and 32 women. The choice of case and the conditions under which they were treated were no different from those under the now familiar tolbutamide therapy. Only 3 patients were under 50 years of age. 23 patients had been diabetic for less than two years and 20 for longer, up to 23 years; previous treatment had been by insulin in 21, tolbutamide in 3, and diet alone in 19.

Dosage.—In the earlier cases 0·5 g. of chlorpropamide was given three times a day after food, with a smaller maintenance dose. As our experience increased, the initial dose was reduced and the later cases in the series received only 0·5 g. or 0·2 g. daily in a single dose after breakfast. A fall in blood-sugar to below 200 mg. per 100 ml. occurred in 38 cases and was maintained at a satisfactory level. Actual hypoglycæmic symptoms were recognised in 1 case only. In 6 patients there was inadequate or no hypoglycæmic effect, and in 1 man who appeared to be doing well an intercurrent bladder infection associated with a carcinoma necessitated a return to insulin in high dosage.

Of the 14 diabetics still maintained on an appropriate diet and chlorpropamide, only 1 is taking more than 0·5 g., and it is possible that those taking less may eventually be controlled on diet alone. 3 of the patients who later responded satisfactorily suffered considerable nausea, anorexia, and burning epigastric pain until the dose was reduced.

Reasons for discontinuing treatment.—The hypoglycæmic effect was inadequate in 6 cases (16%). Intercurrent infection or other illness made it imperative to return to well-tried and predictable methods of treatment in 4 cases. In 7 new diabetics when chlorpropamide had been used for initial control, diet only was the method of final choice. Since my earlier brief report to the International Diabetes Federation in Dusseldorf in July, mentioning the toxic effects we had observed, 4 other cases have occurred on low dosage of the drug. Nausea, anorexia, and vomiting were unpleasant in 15 patients, and in 9 of these vertigo was severe and nystagmus was demonstrable. Dermatitis occurred in 2 patients, associated depression and insomnia was particularly marked in one man, although he gave full credit to the drug for having rid him of his glycosuria. One woman persevered but eventually admitted that however much she disliked having injections of insulin it did not make her feel sick like the tablets. A man of 72 who had been transferred from tolbutamide to chlorpropamide with moderate success for three months suddenly began to vomit and continued for three days until the drug was completely withdrawn.

It is possible that these symptoms may be more severe in ambulatory patients than in a trial conducted on inpatients, but such are the conditions in which such a drug would come to be used. It was found that there was a lowering of the total leucocyte count, but when differential counts were performed no reduction of the polymorphs was noted.

Leicester. JOAN B. WALKER.

CHILDREN IN HOSPITAL

SIR,—As a psychologist and psychiatrist working in a long-term hospital (mainly orthopædic) for children, we should like to make a few comments on Professor Illingworth's article (July 26) and subsequent correspondence.

Everyone would agree that contacts between children and their families should be maintained as far as is reasonably possible. We cannot lay down any general rules because we simply do not know whether the advantages to the children and parents of frequent visiting outweigh the disadvantages in terms of parental anxiety, neglect of other children and husbands, and the unhappiness of unvisited child patients.

The advocates of frequent visiting at all costs seem to base their claim largely on the careful work of Bowlby et al.[1] But Bowlby and his coworkers were not concerned with the effects of visiting on children in hospital. The implicit assumption by those who base their claims for frequent visiting on Bowlby's findings seems to be that frequent visiting will at least alleviate the separation anxiety of mother and child. This seems commonsense, but it may be an unwarrantable jump (cf. the differing views of experts on this point).

It seems to us legitimate to assume that very frequent visiting of all the children in a long-stay hospital (especially when, as at Chailey, patients come from all over the British Isles) is not possible. O'Connor[2] writes: "There is some danger that too great stress on the dangers of mother-child separation may divert interest from the development of research into the optimal cultural conditions for infant intellectual and emotional growth." Similarly, too much stress on mother-child relationships in hospital may divert attention from developing the optimal conditions for children, particularly in long-stay hospitals. Some children are not in fact permanently damaged by early separation from their homes—36% of Bowlby's sample were rated as "adjusted" after their return from hospital, and many of those rated as "maladjusted" showed milder symptoms than was expected. It has been found that some institutions have a beneficial effect on children. It should perhaps be remembered that the basic assumption underlying the present policy of the school health service for the rehabilitation of maladjusted children in hostels and residential schools is that emotional damage in a child can be repaired away from home.

The effect of deprivation in early childhood may not be as lasting as was at first thought. Work with the rehabilitation

1. Walker, J. B. *Brit. med. J.* 1956, ii, 657.

1. Bowlby, J. Maternal Care and Mental Health: W.H.O. Monograph Series No. 2. Geneva, 1951. Bowlby, J., Ainsworth, M., Boston, M., Rosenbluth, D. *Brit. J. med. Psychol.* 1956, **29**, 211.
2. O'Connor, N. *Acta psychol.* 1956, **12**, 174.

of young adult defectives supports this.[3] Given a sound environment, children tend to adapt. Illingworth stresses the importance of gearing hospitals to the needs of children and makes important suggestions on training personnel and on equipment.

There appear to us to be two lines of approach to this problem. One is to gear the hospital to all the needs of children, as far as we know these at present; the other is to try to influence public opinion so that there is in general a more favourable attitude towards the physically handicapped. It has been shown in America that physically handicapped children tend to show more psychological difficulties than physically normal children, irrespective of their placement, and one reason suggested is society's attitude towards the physically handicapped.[4] Bowlby knew that his findings might be at least partially accounted for by the psychological effects of illness per se.

To sum up: there is some evidence to suggest that some children in hospital are not adversely affected emotionally, that some institutional placements can have a beneficial effect on development, and that unfortunate early experiences (including separation or admission to hospital) do not always have irreversible damaging effects. The development of optimal conditions for children in long-term hospitals can do much to minimise psychological trauma. The dangers of separation due to illness can be over-emphasised, and so cause avoidable distress to families and to hospital staffs.

Chailey Heritage
(Craft School and Hospital),
Chailey, Sussex.

ELSPETH STEPHEN
ELIZABETH WHATLEY.

ACADEMIC REVOKE

SIR,—One of Dr. Spencer's conclusions (Aug. 30)—namely, that students displaying academic revoke are predominantly of fat and muscular physique—hardly seems to follow from the data which he presents.

Referring to his fig. 1 he observes: "It will be seen at a glance how work revokers congregate to the left of the somatotype chart." Simple counting of the cases to the left and right of the vertical line yielded 11 revokers to the left, 10 to the right, and 1 on the midline.

If it was intended that the left and right were to be taken from perpendiculars to the ectomorphy axis, the figures on my counting are as follows:

	Revokers	*Other psychiatric cases*
Ectopenic	13	26
Ectomorphic	9	52

This table yields a χ^2 of 4·79, which is significant at the 0·05 level,[1] and which confirms Dr. Spencer's claim of an association between a fat and muscular physique (ectopenia) and the tendency to revoke. This, however, is true of his *particular sample*, and cursory examination of his fig. 1 as well of the above table makes it clear that his population of psychiatric cases is predominantly of ectomorphic physique. Any group of cases of normal physique could therefore be expected to differ from the non-revoke part of his sample.

If Dr. Spencer wished to determine whether his revokers were predominantly of ectopenic physique the appropriate comparison would seem to be:

	Revokers	*Expected numbers (on a 50 : 50 basis)*
Ectopenic	13	11
Ectomorphic	9	11

This table yields a χ^2 of 0·73, which indicates roughly a 40% probability [5] of obtaining a greater proportion of ectopenics on subsequent sampling of a population, where the true incidence of ectopenics and ectomorphics is equal. Hence we cannot conclude that the revokers tend to be any more ectopenic than ectomorphic, and must conclude, on the evidence presented, that they are of normal physique in these respects, as contrasted with the other types of psychiatric cases.

Similar considerations could well apply to the relationship between academic revoke and extroversion. If extroversion is associated with ectopenia, and intraversion with ectomorphy, then a group of normal physique could be expected to be more extroverted than a psychiatric group of predominantly ectomorphic physique.

In conclusion, Dr. Spencer has shown that academic revokers differ from other student psychiatric patients in certain respects. It does not follow that revokers would differ from students in general, in these respects, nor that the correlations would hold good in a general sample of students.

Child Study Centre,
41, Brunswick Square,
London, W.C.1.

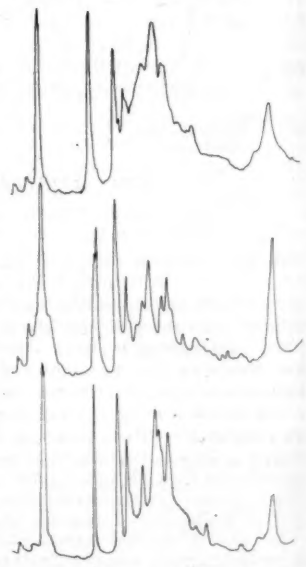
COLIN B. HINDLEY.

3. Clarke, A. D. B., Clarke, A. M. *Brit. J. Psychol.* 1954, **45**, 173.
4. Meyerson, L. *in* Psychology of Exceptional Children and Youth (edited by W. Cruikshank). London, 1956.
5. Fisher, R. A., Yates, F. Statistical Tables. Edinburgh, 1953.

BACTERIAL RESIDUES IN SARCOID LESIONS

SIR,—Mr. Nethercott and Dr. Strawbridge [1] stated that they had demonstrated mycolic acid in extracts of sarcoid lymph-node. This identification was based in part on the acid-fast nature of the extract and in part on a spectroscopic similarity between the extract and a substance called wax C of the human strain of tubercle bacilli.

From experience we have gained in the fractionation of the lipids of many strains of tubercle bacilli and in the identification of the isolated components by means of their infra-red absorption spectra,[2] we feel that insufficient evidence has been presented for the identification of mycolic acid in the extracts of sarcoid lymph-nodes.



Infra-red absorption spectra of various lipid substances: Top, lipid extract of lymph-node from leukæmic individual; middle, mycolic acid; lower, phthiocerol dimycocerosate.

The infra-red spectrum of wax C recorded in the paper of Nethercott and Strawbridge is readily identified as phthiocerol dimycocerosate and contains no apparent mycolic acid. The spectrum of the lymph-node extract is similar to the spectrum of any triglyceride of the type found in lard or butter. To further illustrate the lack of specificity of the compound isolated from sarcoid tissue, we have prepared a similar extract from lymph-node in a case where the postmortem diagnosis was acute leukæmia. A sample of abdominal fat was also extracted. The infra-red absorption spectrum for the lymph-node extract is shown in the accompanying figure together with spectra of phthiocerol dimycocerosate and mycolic acid. The spectra of these three substances are sufficiently reproducible for it to be readily stated that they are three distinct substances each of which can be recognised by its characteristic spectrum. The spectrum of abdominal fat (not shown) was similar to that of the lymph-node extract.

1. Nethercott, S. E., Strawbridge, W. G. *Lancet*, 1956, ii, 1132.
2. Smith, D. W., Randall, H. M., Gastambide-Odier, M. M., Koevoet, A. L. *Ann. N.Y. Acad. Sci.* 1957, **69**, 145.

Concerning the identification of the presence of mycolic acid by staining techniques, we have stained by the hot-carbol-fuchsin method the following substances: phthiocerol dimycocerosate, butter, petrolatum (M.P. 52–56°C), carbowax (M.P. 34–38°C), lecithin, boiled linseed oil, collodion, paraffin, mineral oil, and cholesterol. We find that the following substances resist decoloration by acid alcohol and therefore are acid-fast: petrolatum (M.P. 52–56°C), boiled linseed oil, and collodion.

On the basis of these observations we believe that Mr. Nethercott and Dr. Strawbridge have presented insufficient evidence to prove that mycolic acid has been detected in extracts of sarcoid lymph-node.

D. W. SMITH
H. M. RANDALL.
University of Wisconsin.

PROTECTION OF GONADS FROM RADIATION

SIR,—The article by Mr. Newman in your issue of Sept. 6 on slipping of the upper femoral epiphysis was an interesting reminder of the necessity for taking the so-called lateral (or "frog's leg" position) radiograph in painful conditions of the hip in children.

May I, Sir, make a plea for more protection of the gonads from radiation in these cases?

My practice is to take a normal anteroposterior film without protection, as some of these difficult cases turn out to be an osteochondritis of the ischiopubic ramal junction. All subsequent films, including the first "lateral" view taken, have some screening of the gonads. This screening does not detract from the quality and usefulness of these subsequent radiographs. All follow-up films of the hip, and the films taken at the time of the pinning operation, should have gonadal screening.

M. W. P. WARD.
General Hospital, Harrogate.

ACCIDENTAL HYPOTHERMIA

SIR,—I have recently seen a case of endogenous hypothermia (rectal temperature 84·5° F) in a woman of 45 years with schizophrenia. She had been admitted to hospital with a provisional diagnosis of myxœdema coma. I was struck by the similarity of the clinical picture to that described by Dr. Emslie-Smith (Sept. 6). It would be interesting to know if his patient had a family or personal history of mental illness or if schizophrenia was one of the provisional diagnoses made during the course of her illness.

Though the diagnosis in our case was unequivocal from the clinical, biochemical, and necropsy findings, we did, at the time, regard the electrocardiogram with its high-voltage complexes and upright T waves as further evidence against a diagnosis of myxœdema coma. Thanks to Dr. Emslie-Smith's paper it is now clear that the tracing with its broad-based QRS complexes and J deflections was, in fact, the classical tracing of hypothermia and nothing more. It is a remarkable finding that hypothermia should render the electrocardiogram so specific in some respects and yet so non-specific in others that the pathognomonic appearance of euthermic myxœdema coma is lost.

Though one can have no real objection to the inclusion of myxœdema hypothermias under the general heading of "accidental", since the term means happening by chance or undesigned, as distinct from induced or artificial forms of hypothermia, nevertheless one cannot help but have some misgivings on the ground of possible ambiguity. The term "accidental" has a certain subconscious association with an accident because an accident is a common cause of an accidental occurrence, and the original cases described under the term were examples of exogenous hypothermia following on some accident, either sudden external trauma or sudden internal catastrophe. When one speaks of myxœdema hypothermias one understands endogenous hypothermias, unless stated to the contrary, and in grouping them under the same heading as exogenous hypothermias there is danger, firstly, of thinking myxœdema hypothermias to be of the exposure variety and, secondly, of concluding in general terms about two essentially different forms of hypothermia. Particularly is this so in relation to the question of warming.

The ever-increasing reports on various types of hypothermia make a classification of the subject desirable and suggest a classification of adult hypothermia on more fundamental lines than induced and accidental. Hypothermia may be divided into endogenous and exogenous varieties. Endogenous can be subdivided into types due to central nervous dysfunction and types due to endocrine gland dysfunction. Exogenous can be subdivided into natural (or spontaneous) and artificial (or induced or therapeutic). Natural can be further subdivided into immersion and exposure types and artificial into medical and surgical types. The exogenous hypothermia due to natural exposure would correspond with the cases originally described under "accidental".

DONOUGH MOYLAN.
Coventry.

INDUSTRIAL MEDICINE AND GENERAL PRACTICE

SIR,—I read Dr. Keatinge's letter in your issue of Sept. 6 with interest because I felt that the leading article in *The Times* of Aug. 4 was very special pleading. It suggests that the Harlow scheme could be adopted for most towns in which are small industrial units and emphasises the advantage of general practitioners thus looking after their own patients.

Harlow is a small new centre with work, home, and doctor closely knit. In most areas of this country the scatter is wide. Most general practitioners doing industrial work would inevitably be looking after the patients of other doctors. In many families today members are registered with different doctors, and in a group practice, which is recommended, a group of doctors look after the same family. In this development where does the family doctor come in?

The Times article makes no reference to the duties of the appointed factory doctor. This statutory work accounts for a major part of the time of general practitioners spent in industry, and has aroused considerable criticism, though the work presents unique opportunities for the advancement of health. I venture to refer to my own study [1] of this problem, concerning which the King George's Jubilee Trust in their report *Citizens of Tomorrow* recorded: "... it seemed to us that national development might well be based on a pilot scheme of this nature."

Finally, reference is made to the need for whole-time medical officers in the larger firms to study toxic hazards and environmental conditions, but there is no mention of the need for these problems to be met by occupational hygiene laboratories working on a regional basis, preferably associated with a university. This has been done in the U.S.A. and other countries. Expert advice is then readily available for all doctors working in industry or elsewhere and also for employers and even employees who think their health may be affected by environmental conditions.

M. E. M. HERFORD.
Farnham Royal, Bucks.

1. Herford, M. E. M. Youth at Work. London, 1957.

THE FRONTIERS OF MEDICINE

SIR,—I have read with interest Prof. C. H. Stuart-Harris' article of Aug. 30: like those of the celebrated egg, parts of it are excellent; but I resent very deeply his statement "When I was a student, it was common to feel that patients were admitted to the medical wards to lie and rot. The great watch-word was 'masterly inactivity' . . ." (Dr. Stuart-Harris qualified as recently as 1931.) I should like to ask him (a) whether his insult is intended only for the physicians of the hospital where he was a student or for British physicians in general, and (b) whether he thinks that his opinion is widely shared by the large numbers of whole-time professors and lecturers who are now mainly responsible for the training of young doctors.

Belfast. ROBERT MARSHALL.

ATTEMPTED SUICIDE

SIR,—It is impossible for authors to defend themselves against an anonymous review, even if they feel that their work has not received a fair appraisal. They have, however, the right to protest against misquotations. I am referring to the review (Sept. 6) of the book *Attempted Suicide*. In this and other books the term "suicidal act" has been used for both suicide and attempted suicide. According to your review it was used only for the latter, which is quoted as having been regarded by the authors as not self-destructive. No such nonsense was asserted in the book. On the contrary, it was made quite clear that every suicidal act aimed at self-destruction but that the suicidal attempt could not be fully understood if this motivation alone was taken into consideration.

Sheffield, 10. E. STENGEL.

*** We much regret that our brief summary of the views of Professor Stengel and Miss Cook should have misrepresented them. Most authors will sympathise with him about the difficulty of defence against criticism in review; but this is no greater when the review is editorial than when it is personal. Our reviews, like our annotations and leaders, can be challenged.—ED. L.

EFFECT OF INACTIVATED SERUM ON COLD AGGLUTININS

SIR,—From the studies of Boorman and Dodd [1] we learn that human serum can enhance the activity of immune isoantibodies when it is used as a diluent instead of saline. Also in other immune systems (immune serum anti-sheep-red-cells or in Rose's test for rheumatoid arthritis) human serum reveals this property. I have investigated whether normal human serum retains this property also in the titration of autoantibodies, and I chose the cold agglutinins as more readily titrable.

If fresh serum is used instead of saline, the titre of the cold agglutinins increases but little; while if a previously inactivated (at 56°C for 30 min.) serum is used, there is a huge increase in the titre (from 1 : 4000 to 1 : 16 million in one case, and from 1 : 1000 to 1 : 4000 in another).

The use of albumin or human gamma-globulin instead of serum does not bring about the phenomenon. Serums devoid of properdin have given similar results, as have also normal serums that have not been inactivated but kept at −20°C for one to two months.

Not all human serums show this considerable activation of the autoantibody titre: some, in fact, are incapable of producing it, while others increase the titre only slightly.

It has not so far been possible to discover whether the phenomenon is due to the presence of an activator or the disappearance of a serum inhibitor: any such inhibitor, which disappears at a temperature of 56°C maintained for 30 min. may be represented by a heat-labile fraction of the complement (C^1 or C^2) which is destroyed at that temperature.

Institute of Medical Pathology, University of Genoa. V. ROSSI.

INTRAGASTRIC INFUSION

SIR,—In 1956, you were good enough to publish a short communication [1] about intragastric infusion in infants with acute dyspepsia.

We have now used this method 140 times in infants, mainly for acute gastroenteritis. We gave physiological saline, Ringer's or Darrow's solutions, and 5% glucose solution, the amount and proportions being the same as for parenteral infusions. Sometimes we added plasma substitutes. Sometimes plasma was given intravenously. In milder cases gastric infusion was combined with feeding by mouth or through the tube. We used polyethylene and rubber tubes, as thin as possible, passed through the nose. We have not seen any serious complications, even after leaving the tube in for several days.

The effect on vomiting was striking. In severe gastroenteritis the rehydratation was often slower than by the intravenous route, but sometimes the result was almost equally good. In toxic gastroenteritis gastric infusion was used only after improvement had been achieved by intravenous infusion. Several times we had to replace the method by the intravenous one; either it was not suitable at all or the composition of fluids was wrong.

Intragastric infusion has proved a valuable therapeutic measure, and vomiting of any origin very seldom resists this treatment. I should be glad to hear from any of your readers who have had experience of enteral infusions.

State Hospital, Children's Department, Děčín, Czechoslovakia. S. J. HAVELKA.

CARDIAC OUTPUT AND RENAL BLOOD-FLOW IN SEVERE DEHYDRATION

SIR,—It is generally supposed that an inadequate general circulation is associated with a reduction in renal blood-flow which is disproportionate to the reduction in cardiac output. Renal blood-flow has been determined in most cases by the clearance technique, though this seems an unreliable method when the diuresis is low, as in dehydration.

We compared, in serial simultaneous determinations, the cardiac output (by the dye-dilution technique) and the renal blood-flow (by measuring directly the renal venous outflow) in narcotised dogs dehydrated by ligating the pylorus 72 hours before the experiment. The reduction in cardiac output was greater than expected from the fall in arterial pressure, so that the total peripheral resistance had increased. As determined by the direct technique there was a small decrease in the absolute value of renal blood-flow and the calculated renal vascular resistance was somewhat increased. The decrease in renal blood-flow was nearly proportional to the diminished cardiac output.

Thus the renal fraction of cardiac output did not decrease during dehydration, as compared to the renal fraction determined by the same technique in normal dogs. On the basis of the *p*-aminohippuric acid clearance and extraction ratio a substantially reduced renal fraction was found. The clearance results suggested a nearly total renal ischæmia and an enormous increase in renal vascular resistance.

A detailed account of our data is to be published in *Acta medica hungarica*.

Physiological Institute, Medical University, Budapest. P. BÁLINT J. STURCZ.

1. Boorman, K. E., Dodd, B. E. *J. Path. Bact.* 1947, **59**, 95.

1. Havelka, S. J. *Lancet*, 1956, ii, 1312.

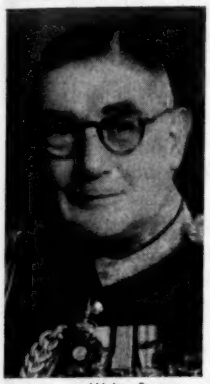
Obituary

JAMES BENNETT HANCE

K.C.M.G., K.C.I.E., O.B.E., M.A., M.D. Cantab., F.R.C.S.E.

Sir Bennett Hance, whose death we announced last week, was already known throughout India as a surgeon and clinician before promotion in 1940 brought him to administrative rank. His success in this new sphere was recognised by his appointment as director-general of the Indian Medical Service in 1943. His successful tenure of that post ended with the British withdrawal from India, but he continued his work for both countries as medical adviser to the Commonwealth Relations Office.

He was born at Liscard, Cheshire, in 1887, the son of a Liverpool barrister, and he was educated at Oundle School, Cambridge University, and Guy's Hospital. After qualifying in 1911 he spent some time in Liverpool as assistant to Prof. Blair Bell, who fostered his interest in gynæcology. In 1912 he entered the Indian Medical Service with the hope of becoming a teaching gynæcologist on the civil side of the service. But the 1914–18 war upset this plan, and after service in France and with the South Persian Expeditionary Force he joined the Foreign and Political Department. As a result he spent the greater part of his service in Waziristan, on the North West Frontier, and in the Princely States of Jodhpur, Rajkot, and Mysore. While he was resident surgeon in Mysore his chief hospital was at Bangalore, where he tackled not only his favourite gynæcological problems but also all branches of major surgery, including his latest enthusiasm—orthopædics. In 1940 the clinician reluctantly gave way to the administrator, and he entered British India, almost as a stranger, to become inspector-general of civil hospitals in Central India. In 1942 he was moved to Delhi as deputy director-general of the I.M.S., when his administrative gifts were quickly recognised; and a year later he succeeded Sir Gordon Jolly as director-general.



Walter Stoneman

Even in the midst of war Hance recognised the importance of post-war reconstruction, and he was a member of the Bhore Commission on the health services of India. He visited the United States to study American methods of medical education, and he returned to India to help to plan the Postgraduate Medical Institute at Delhi. After his return to this country his work at the Commonwealth Relations Office was interrupted so that he could advise on the organisation of the health services of Ceylon under the Colombo plan. Despite ill health he continued to work steadily and devotedly. He died on Sept. 5 at the end of an assignment abroad.

He was appointed C.I.E. in 1939, promoted K.C.I.E. in 1946, and created K.C.M.G. in 1953.

G. R. McR. writes:

"Bennett Hance had a zest for life. He was ever vital and full of enthusiasm. When I met him first in 1924 in Dera Ismail Khan he was experimenting with a new lamp which he had designed for carrying out blood-sugar estimation by McLean's method, and that only a few months after the introduction of insulin. He had just finished a five-hour operation session. I saw him again that evening; the floor of his living-room was covered with plans for new dispensaries in his wild remote frontier charge, his table with piles of figures for his annual drug and equipment estimates. It was, I found, typical of the man—a day's work measured only by what could be squeezed into it. He was an all-rounder, as ready to tackle a cholera epidemic as a Wertheim operation or an iridectomy. His years in Persia provided him with a fund of Persian proverbs, which he quoted freely. His service in Waziristan first brought him into contact with the wild Pathans, and he became a fluent speaker of Pushtu. The Pathan servants whom he engaged there remained in his entourage throughout the rest of his service—strange and fearsome though they were among the gentler minions of Mysore.

"On his retirement from the post of director-general it was recognised that he had been one of the greatest holders of that post, for he had not only coped well with the great immediate problems of war-time India but had drawn up sound plans for reconstruction and progress in post-war independent India—plans which are working well today. Over eleven years ago his left lung was removed for proved carcinoma. Within three months he was back in harness, touring the world, planning, inspecting, and again planning. As medical adviser in the Commonwealth Relations Office his dogged devotion to duty when hardly able to draw breath was marvelled at by all—he was always cheerful. His end came suddenly and peacefully, on a brief holiday after an important mission oversea. His brother officers will ever be grateful for the trouble he took over their resettlement: hosts of students from oversea, patiently interviewed and placed by him for training under the Colombo plan, share that gratitude for the work of Bennett Hance."

By his first wife, Catherine, daughter of the late Dr. C. L. Leonard of Philadelphia, Sir Bennett had two daughters. In 1938 he married as his second wife Frau Richildis von Kaan, daughter of Richard von Warton of Vienna, who survives him.

WILLIAM MOWLL FRAZER

O.B.E., M.D., M.Sc. Lpool, D.P.H.

Prof. W. M. Frazer, whose death on Sept. 8 we announced last week, was medical officer of health of the city and port of Liverpool from 1931 to 1953.

He was born in 1888 in Liverpool and was educated at Liverpool and London Universities. He took his M.SC. in 1909, but his medical studies were interrupted by the 1914–18 war, during which he served in the King's (Liverpool) Regiment. Afterwards he returned to Liverpool University and qualified in 1921. The following year he took the D.P.H., for he had already chosen public health as his specialty. He held appointments as assistant M.O.H. at Blackburn, and as M.O.H. at Dewsbury and Hull before he returned in 1931 to Liverpool as M.O.H. Two years later he was appointed to the chair of public health at the University.

His work in Liverpool centred round the city's hospital service, and it was largely thanks to him that at the outbreak of war in 1939 the Liverpool municipal hospitals were able not only to cope efficiently with the heavy civilian casualties of the city but also to help to care for the Service casualties who were brought to the port from overseas.

For his work in Civil Defence he was appointed O.B.E. in 1939, and during the war he was responsible for the Liverpool casualty services, together with the billeting services, which were sorely tried during the aerial bombardment of 1940 and 1941. He served on committees set up by the Ministry of Health and the Medical Research Council, and on the health committee of the Association of Municipal Corporations. He gave the Chadwick and Newsholme lectures, and in 1942 visited the United States to lecture on public health at the request of the Ministry of Information. A prolific and gifted writer, he will be particularly remembered for his monograph *Duncan of Liverpool* (1947), his *Textbook of Public Health* (the earlier

editions appeared with C. O. Stallybrass as coauthor), and his *History of English Public Health* (1950).

Frazer had always encouraged cooperation between the municipal and teaching hospitals, and he believed in the use of all hospitals for training students. It was he who had suggested to the Vice-Chancellor of the University the formation of the Liverpool Hospitals Joint Advisory Committee and who had put forward the suggestion to found a chair in child health. As a result of his influence, when the National Health Service was started the regional hospital board took over from the city hospitals, which were as well organised as any in the country. Of his continuing work for the hospital services T. L. H., one of his old students, writes:

"It was with understandable reluctance that Frazer contemplated the handing over of the city hospitals to the Regional Board. Nevertheless, he entered wholeheartedly into the work of the board and was justifiably proud that he was the only medical officer of health who had been appointed initially to membership of the board at the outset of the National Health Service. He was also appointed to the Board of Governors of the United Liverpool Hospitals, and by a deliberate piece of inspired cooperation by both boards was appointed chairman of their respective establishment committees. In this key position on the two boards he was able to help further in drawing together the teaching and regional hospitals in the new service. He was acceptable to the local-authority representatives and yet fully understood the approach of the medical members, and he exerted an integrating influence which helped in the early days to knit the members of the board into a team.

"In these formative early years of the N.H.S., though still an active medical officer of health, he gave a great deal of his time to this work, and after his retirement in 1953 he spent more and more of his time on committee and board work. It was not only in the field of establishment and appointments that he gave of his knowledge and experience; his advice was also constantly sought on re-planning the hospitals in the region. His local-authority affinities naturally gave a bias to his views, but he was always ready to accept the inevitabilities of the changed circumstances. As an experienced medical administrator he was a staunch friend of those who found the present organisation a little irksome and unfamiliar, and his ready support was always greatly valued. His special experience and local knowledge will be difficult to replace."

Another colleague, A. S., writes:

"Frazer was a man of high principles and had a strict ethical code. He will long be remembered, not merely for his outstanding academic merit, brilliance of intellect, and phenomenal memory, but also for his calm and resolute approach to administrative problems. He was essentially a thinker who reached his conclusions by logical deduction, and, having decided what was right, he was prepared to support his opinion in the face of the most resolute opposition. He was a reliable source of information and advice, and was always prepared to discuss administrative problems with his juniors and also to give them the advantage of his thoughts on any matters of concern."

Professor Frazer leaves a widow and a married son and daughter, both of whom graduated in medicine at Liverpool University.

DAVID JUSTIN DAVIES

M.B. Lond., F.F.A. R.C.S., D.A.

Dr. Justin Davies, consultant anæsthetist to the Royal Infirmary and General Hospital in Leicester, died on Sept. 7, while playing golf. He was 61 years of age.

He studied medicine at Cardiff and in London at the Middlesex Hospital, qualifying in 1920. After holding resident posts at the Middlesex and at Leicester Royal Infirmary he set up in practice in Leicester with his wife. He became interested in anæsthetics and decided to make that his specialty, and he was appointed visiting anæsthetist to Leicester Royal Infirmary in 1933. He quickly built up an extensive hospital and private practice. He was a vice-president of the Leicester Medical Society, and a former president of the Sheffield and East Midland Society of Anæsthetists. A keen Territorial, he held the rank of lieut.-colonel in the R.A.M.C. He commanded the no. 9 C.C.S., which went to France in 1939, but he was invalided out of the Service after Dunkirk. He was elected F.F.A. R.C.S. in 1953.

R. McD. C. writes:

"Justin Davies was a most likeable man and extremely popular. He had a wide circle of friends, all of whom will miss very much his genial and engaging personality. Recently he had been in failing health, and he fully realised the import of his physical handicaps. Himself a son of the manse, he took a deep interest in the affairs of the presbyterian church in Leicester, of which he was an elder. He developed a most admirable philosophical attitude to life, and was determined to carry on with his work. Nothing gave him more pleasure than a quiet game of golf with his friends, and one cannot help feeling that the end, coming as it did, might well have been the one he himself would have chosen."

Dr. Davies married Dr. Lucy Simpson, who died in 1947. Their daughter is a final-year medical student.

HENRY BUCKLEY RODERICK

O.B.E., T.D., M.A., M.D., M.Chir. Cantab., F.R.C.S.

Dr. Roderick died in Cambridge on Aug. 29 at the age of 84, nearly sixty years after the beginning of his medical work in East Anglia.

He was born in Llanelly in 1874, the son of William Roderick, and he was educated at Bath College and at Emmanuel College, Cambridge, taking his B.A. with honours in 1894. He finished his clinical studies at St. George's Hospital where, after qualifying in 1898, he was appointed surgical registrar. He returned to Cambridge in 1900 to enter general practice, and a year later he was appointed to a demonstratorship of surgery in the university medical school, to assist Mr. Joseph Griffiths, who, after the death of Sir George Humphrey, was acting as deputy professor of surgery. Roderick later assisted Mr. Howard Marsh when he was appointed to the professorship in 1903. After Marsh died in 1915, the professorship was suspended, but Roderick continued as a demonstrator, lecturing in surgery and surgical pathology until 1926. Two years later he was appointed supervisor and examiner in surgery.

In 1901 he became medical officer to the University Rifle Volunteers, and seven years later he was appointed commanding officer of the medical contingent of the University O.T.C. In 1914 he joined the First Eastern General Hospital, R.A.M.C. T.A., with the rank of major; and later he went to France, with the rank of lieut.-colonel, to command the 55th General Hospital. He was twice mentioned in despatches, was appointed O.B.E., and was awarded the T.D.

In 1919 he returned to Cambridge, and was appointed honorary surgeon to Addenbrooke's Hospital. Although essentially a general surgeon, he was especially interested in orthopædics and he at once began to promote this specialty in the area. He started special orthopædic clinics in Addenbrooke's Hospital, and with the help of the British Red Cross he organised orthopædic clinics in the country and at Wisbech and Huntingdon Hospitals. In 1932 he was elected F.R.C.S. as a member of twenty years' standing. In 1939 he should have retired from the active hospital staff, but with willingness and energy he carried on until the return of his colleagues from

military service, when with characteristic modesty he stood down.

Of his work for orthopædics in East Anglia A. S. H. W. writes:

"By his hard work and enthusiasm Roderick stimulated public interest in the prevention and treatment of crippling diseases, and to these efforts are owed the foundations from which the present orthopædic services have grown. His constant campaigning to establish a long-stay orthopædic hospital never came to full fruition, but as a result of his efforts the need was seen, and regional reorganisation under the E.M.S. and N.H.S. has to some extent fulfilled this want.

"Outside his profession he had many interests. For many years he was churchwarden at Great St. Mary's. He was an ardent Freemason, past grand deacon of England and a past deputy provincial grand master. He was a founder and past president of the Cambridge rotary club, and a past president of the Cambridge branch of the British Legion. But this list of interests and appointments does not give a true picture of the real Roderick, whose outstanding characteristics were gentle humour, genuine kindliness, and a wonderful capacity for making friends."

In 1908 he married Hilda, daughter of John Clay, of Cambridge. She survives him with three daughters and three sons. Their fourth son was killed in the war.

ROBERT RUTHERFORD

O.B.E., T.D., F.R.C.S.

Mr. Robert Rutherford died on Aug. 19 at his home at Longtown, Cumberland, at the age of 63. His years of practice there were interrupted by distinguished service in the late war for which he was appointed O.B.E. in 1946.

He was born in Glasgow, but his family moved a few years later to Carlisle and he went to school there at Grosvenor College. He was apprenticed to a chemist in Carlisle, but after serving with the Black Watch during the 1914–18 war he began to study medicine at King's College Hospital. After qualifying in 1927 he held house-appointments at King's, and in 1930 he took the F.R.C.S. The same year he was appointed clinical director of Hillingdon County Hospital. In 1934 he returned to Cumberland and settled in practice at Longtown. He was also for some years obstetric consultant to Cumberland County Council.

In 1939 as a Territorial officer he was recalled at once. He served throughout the war, commanding military hospitals in Palestine and India. In 1944 he was in charge of the surgical division of the 10th British General Hospital in Normandy and Belgium, where he took part in the early clinical trials of penicillin. Besides being appointed O.B.E., he was mentioned in dispatches and was awarded the T.D. After the war he returned to his practice and also acted as medical officer to the Westmorland and Cumberland Yeomanry. He retired from the Territorial Army in 1952 with the rank of colonel.

He married in 1931 Miss Nora Borrett, and she survives him with two sons and three daughters.

Appointments

HISCOCK, WINIFRED M., L.R.C.P.E.: deputy M.O.H. and school M.O., Swindon.

HUNTER, A. H. D., M.B. Glasg., D.P.M.: consultant psychiatrist to be designated medical superintendent, Kingsway Hospital, Derby.

SPEIRS, N. T., M.B., B.SC. Edin., D.M.R.D.: part-time consultant radiologist, Princess Margaret Rose Hospital, Edenhall Hospital, and the Royal Edinburgh Mental Hospitals.

Births, Marriages, and Deaths

JAMES.—On Sept. 15, at Hammersmith Hospital, to Dr. Sheila Sherlock, wife of Dr. D. Geraint James—a daughter.

Notes and News

FUTURE OF DISTRICT NURSING

IN opening the headquarters of the Croydon District Nursing Association on Sept. 15, Mr. Derek Walker-Smith, the Minister of Health, said that it was the "first purpose-built administration centre for district nursing to be opened since the war". Home nursing was an important part of the health service, and he had had reports from several areas that up to 2 bed-day's per patient had been saved by the preparation of patients for operations and by diagnostic procedures carried out at home. A Lancashire hospital had saved 4 bed-days per patient by discharging patients earlier to the care of the general practitioner and district nurse. He believed that many more hospitals could discharge patients earlier to the care of the home health service if they made it a rule to inform the general practitioner and the local authority health service of the date of discharge and treatment, and if the local health authority provided a good home-help service and adequate sick-room equipment. In England and Wales during 1957 home nurses had dealt with 1 million patients and made over 25 million visits. Over half of these visits were to patients over sixty-five, and the home nursing service was "a powerful aid" in caring for the elderly and chronic sick.

PUERTO RICANS IN NEW YORK

UNDER the supervision of Dr. Beatrice B. Berle a group of physicians set out to provide limited outpatient care for people in a slum area of New York. Dr. Berle[1] has now described a study of 80 Puerto Rican families, which had come to New York mainly in search of "progress"—a higher standard of living—sometimes in quest of treatment not available in their island home. As in slum communities everywhere, the reaction to dilapidated walls, falling ceilings, and cockroaches varied widely from one family to another. The reasons given for moving by those who found new quarters on their own were chiefly social—to get away from the drug addicts, the badly-behaved adults and children in the neighbourhood. Medical and hospital needs of these families were greater than those of their New York neighbours, particularly in the first year or two after immigration, when they experienced many road accidents and much infectious disease—especially whooping-cough—though losing the risk of chronic reinfection by intestinal parasites. Medical resources available to them included private practitioners (whose usual charge was $3–4 for an office visit and $7–8 for a house call, "some medicine" being usually included in the fee); "welfare doctors", paid by the Department of Welfare to render emergency service where an individual in receipt of public assistance was too ill to go to the outpatient department of a city hospital; the services of the Department of Health, mainly advisory and immunological; and the wards and outpatient departments of city hospitals. A few were entitled to some form of hospital insurance through their unions. Since 1943 Mount Sinai Hospital has operated a reception ward where children are seen by a physician without previous appointment on payment of $1. Dr. Berle strongly urges the establishment of neighbourhood family-centred clinics to supplement overcrowded outpatient departments; here "the family, not the disease, not the individual alone, would be studied and treated as a unit".

THE POSTOPERATIVE BED

Dr. F. Temple Clive draws our attention to some small pieces of equipment which help in the postoperative treatment of patients in their own beds. These are detachable metal holders for oxygen cylinder, blood-transfusion bottle, and under-water drainage bottle. Made of light metal, they are easily fixed to the standard hospital bedstead. Devised at the Preston Hall Chest Hospital, Maidstone, they have been used there for several years.

1. 80 Puerto Rican Families in New York City. By BEATRICE B. BERLE, M.D. New York: Columbia University Press. London: Oxford University Press. 1958. Pp. 331. 38s.

Particulars, including diagrams, may be had from the general manager of British Legion Industries, Preston Hall, Maidstone, Kent.

Royal College of Physicians of London

On Friday, Oct. 17, at 3 P.M., Sir Geoffrey Keynes will give the Harveian oration. His subject will be Harvey through John Aubrey's eyes. On Thursday, Nov. 6, at 5 P.M., Prof. K. W. Donald will give the Bradshaw lecture on heart-disease and exercise. On Tuesday, Nov. 18, at 5 P.M., Dr. Mildred Creak will give the Charles West lecture. The title of her lecture will be Child Health and Child Psychiatry—Neighbours or Colleagues? All the lectures will be given at the college, Pall Mall East, S.W.1.

Association of Clinical Pathologists

This association is holding a meeting from Oct. 2 to 4, at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2. To commemorate the centenary of the publication of Virchow's *Cellular Pathology* the meeting will include a symposium on the pathology of the cell. The speakers will be Sir Roy Cameron, Dr. Joseph Bamforth, Dr. G. R. Osborn, Prof. Robert Cruickshank, Dr. Honor Fell, Prof. N. H. Martin, and Dr. A. G. E. Pearse. Further particulars may be had from Dr. J. N. Cumings, The National Hospital, Queen Square, W.C.1.

M.R.C. Travelling Fellowships

The Medical Research Council invites applications for travelling fellowships for 1959–60.

These fellowships are intended for graduates resident in this country who have had some training in research in clinical medicine or surgery, or in some other branch of medical science, and who are likely to profit by a period of work at a centre in the United States or elsewhere abroad, before taking up appointments for higher teaching or research in the United Kingdom. Fellowships held in the United States will provide maintenance allowances, at rates varying from 3000 to 5000 dollars per annum, and travelling expenses. Forms of application may be had from the secretary of the Council, 38, Old Queen Street, London, S.W.1, and must be returned by Oct. 31.

British Postgraduate Medical Federation

The inaugural lecture of the 1958–59 series on the scientific basis of medicine will be given by Sir Edward Salisbury at 5.30 P.M. on Thursday, Oct. 16, at the Senate House, University of London, Malet Street, W.C.1. His subject will be the influence of botany on health and disease.

Assessment and Education of Cerebral Palsied Children

The British Council for the Welfare of Spastics have arranged a conference on this subject for doctors on Saturday, Nov. 8, at the Engineering School, University Walk, Bristol. Prof. A. V. Neale will be in the chair, and the speakers will include Dr. R. M. Norman, Dr. N. S. Alcock, Dr. G. E. Woods, and Dr. A. L. Smallwood. Tickets (17*s.* 6*d.*) may be had from the secretary of the council, 13, Suffolk Street, Haymarket, London, S.W.1.

Institute of Diseases of the Chest, London

Clinical demonstrations for doctors will be arranged by Dr. E. H. Hudson on Fridays, from Oct. 3 to Dec. 12. Open lectures will be given on Wednesdays, from Oct. 1 to Dec. 10, by Sir Russell Brock, Dr. F. P. Lee Lander, Dr. A. B. Paterson, Dr. J. R. May, Dr. F. H. Scadding, Dr. Paul Wood, Dr. A. M. C. Macpherson, Mr. V. C. Thompson, Dr. N. L. Rusby, Mr. W. P. Cleland, and Mr. Donald Barlow. All the meetings will be held at 5 P.M., at the institute, Brompton Hospital, Fulham Road, S.W.3.

Inhaled Particles and Vapours

A symposium on this subject, arranged by the British Occupational Hygiene Society, will be held in Oxford in April, 1960. Further particulars may be had from Mr. J. S. McLintock, Medical Service, National Coal Board, Hobart House, London, S.W.1.

Society of British Neurological Surgeons

On Wednesday, Oct. 22, at 5.30 P.M., at the London Hospital, Sir Geoffrey Jefferson will give the first Hugh Cairns memorial lecture. He will speak on Sir Hugh Cairns. Tickets may be had from Mr. D. W. C. Northfield at the London Hospital, E.1.

Postgraduate Travelling Fellowships

The governing body of the British Postgraduate Medical Federation is offering a limited number of these fellowships to doctors and dentists. Further particulars will be found in our advertisement columns.

Medical Protection Society

The annual general meeting of this society will be held at Victory House, Leicester Square, London, W.C.2, on Wednesday, Oct. 1, at 3 P.M.

British Society of Dental Radiology

Representatives from the X-ray departments of dental schools and hospitals in the United Kingdom have formed this society under the chairmanship of Dr. Sydney Blackman. Further particulars may be had from Mr. Guy Poyton, X-ray Department, Eastman Dental Hospital, Gray's Inn Road, London, W.C.1.

Royal Medico-Psychological Association

This association is holding a joint meeting with the Section of Psychiatry of the Royal Society of Medicine, at 1, Wimpole Street, London, W.1, on Thursday, Sept. 25, at 5 P.M., when Dr. W. E. Barton, associate professor of psychiatry at Boston University, will speak on research in rehabilitation.

Section of Psychotherapy and Social Psychiatry.—On Wednesday, Sept. 24, at 8 P.M., at 11, Chandos Street, W.1, Mr. Richard Hauser will speak on community developments and group work in psychiatry.

On Friday, Oct. 10, at 5 P.M., Mr. William Doolin will give the opening sessional address of the Faculty of Medicine in the Firth Hall, University of Sheffield. His subject will be *Is* History Bunk?

On Monday, Oct. 6, at 3 P.M., Sir Eric James, high master of Manchester Grammar School, will give the inaugural address of the new session to the faculty of medicine of the University of Birmingham, at Queen Elizabeth Hospital, Edgbaston, Birmingham.

Postgraduate demonstrations in psychiatry will be held at St. George's Hospital Medical School, Hyde Park Corner, London, S.W.1, for doctors on alternate Thursdays from Oct. 9 to Dec. 4 at 5 P.M. Owing to rebuilding the demonstrations in neurology will not be resumed until the Lent term, 1959.

Surgeon Rear-Admiral E. T. S. Rudd has been appointed house governor and medical superintendent of King Edward VII Convalescent Home for Officers, Osborne, in succession to Sir Neil Cantlie.

Lieut.-Colonel C. A. Bozman, director of the Wellcome Museum of Medical Science, has been invited by the World Health Organisation to join a small team of consultants which is to visit the All-India Institute of Public Health and Hygiene in Calcutta.

Dr. B. Cinader has been appointed head of the subdivision of immunochemistry in the Ontario Cancer Institute and associate professor in the department of medical biophysics at the University of Toronto.

Dr. P. W. Hutton, medical specialist at Mulago Hospital, Kampala, Uganda, has been elected president of the Association of Physicians of East Africa.

The address on Moral Responsibility in Clinical Research, by Mr. D. MacG. Jackson, F.R.C.S., which was summarised in our issue of April 26, has now been published in full for the Christian Medical Fellowship, by the Tyndale Press, 39, Bedford Square, London, W.C.1 (pp. 20. 6*d.*).

The annual students' dinner of University College Hospital Medical School will be held at the Savoy Hotel, Strand, London, W.C.2, on Friday, Oct. 24, at 8 P.M. Application for tickets (£1 12*s.* 6*d.*) should be made to the hon. secretary of the students' association at the medical school. Postgraduate demonstrations will be given at the school on Oct. 23 and 24.